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ACTA RADIOLOGICA
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ARTERIOVENOUS FISTULAE OF THE UTERUS AND ADNEXA

An arteriographic study

by

Ulf Borell and *Ingmar Fernström*

Arteriovenous fistulae involving the uterine or adnexal blood vessels are extremely rare, only 7 cases of the former (DUBREUIL and LOUBAT 1926, GRAVES and VAN SMITH 1927, ELKIN and BANNER 1946, REYNOLDS et coll. 1949, GAINES and GREENWALD 1953, WILLIAMS 1954, HOGE 1955) and 1 case of the latter (CAMP 1953) being reported in the literature.

Six of the 7 patients with an uterine arteriovenous fistula had undergone laparotomy on account of uncontrollable vaginal bleeding. At operation a pulsating, slightly enlarged and soft uterus with markedly dilated blood vessels in both parametria were found. In none of these cases was the aetiology of the lesion established. In the case published by ELKIN and BANNER the lesion was diagnosed a few months after hysterectomy had been performed.

In CAMP's case the lesion probably resulted from supravaginal hysterectomy carried out 17 years previously.

According to BURWELL (1938) the normal placenta represents a modified arteriovenous fistula. He arrived at this conclusion from the observa-

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Table I

Contrast filling of veins in pelvic arteriography

Type of case	Number of cases	Veins contrast filled	
		Number of cases	Percentage
Gynaecologic	345	[1] 2	0.6
Obstetric	172	43	25

[1] Filling of normal uterine veins after capillary phase. The diagnosis was salpingitis and ovarian cyst, respectively.

tion that patients with an arteriovenous fistula anywhere in the body show circulatory disturbances which are identical with those found in healthy pregnant women. On the basis of experimental studies in pregnant women BICKERS (1942) supported BURWELL's view whilst SILIQUINI et coll. (1954) argued against it.

In a previous paper (BORELL, FERNSTRÖM and WESTMAN 1955), 2 cases of hydatidiform mole were reported in which pelvic arteriography resulted in the filling of large veins in the uterine wall and parametria. As these veins were visible while the uterine arteries were still filled with contrast medium, the possibility of the presence of abnormal arteriovenous communications involving the placental blood vessels was considered.

During the last few years the authors have encountered a number of cases in which the roentgenographic appearances strongly suggested the presence of abnormal arteriovenous communications involving the uterine or adnexal blood vessels. As these cases are very rare and in view of the fact that pelvic arteriography has hitherto not been used in the diagnosis of this condition, they were considered sufficiently interesting to be recorded.

Material and methods

Pelvic arteriography was carried out in 517 women; 345 of these had a gynaecologic disease and 172 were pregnant. Veins were contrast filled in 45 cases. These form the basis of the present investigation. Tables I and II show the diagnoses in this group.

Pelvic arteriography was performed by the percutaneous retrograde injection method using the instruments devised by SELDINGER (1953). The essential features of this method are briefly as follows (for details the reader is referred to FERNSTRÖM 1955). A polythene catheter is in-

Table II

Contrast filling of veins in cases of normal and abnormal pregnancy

Diagnosis	Number of cases	Veins contrast filled in total number of cases	Veins contrast filled		Abnormal communications (%)	Veins contrast filled after arterial phase
			In early arterial phase	In late arterial phase		
Normal intra-uterine pregnancy	112	18	—	1	0.9	17
Miscarriage and 'missed abortion'	20	7	—	4	20	3
Ectopic pregnancy	35	14	3	7	29	4
Hydatidiform mole	4	3	—	2	—	1
Chorionepithelioma	1	1	1	—	—	—

troduced percutaneously into the femoral artery so that its tip lies just below the bifurcation of the aorta. Both femoral arteries are compressed at the level of the inguinal ligament and 40 to 50 ml of contrast medium are injected rapidly. Three films are generally obtained, the first immediately after completion of the injection and the other two at intervals of two seconds.

For purposes of comparison 50 of the 517 cases in this series were examined by serial roentgenography with 4 to 15 films at intervals of one or two seconds.

Experience has shown that the main trunk of the uterine artery and its larger branches can be demonstrated by pelvic arteriography whilst demonstration of the lesser branches and of the capillaries is not obtained because their calibre is too small. In a few cases the entire uterus was rendered opaque after the arteries were no longer visible. A large number of small uterine blood vessels were probably filled with contrast medium, resulting in visibility of the entire uterus.

The films were considered to be projected in the *arterial phase* when arteries were demonstrated, and in the *capillary phase* when the entire uterus was visible.

In the 45 cases in this series in which veins filled, this happened either during or after the arterial phase.

Contrast filling of the uterine or ovarian veins during the arterial phase was considered to be diagnostic of an arteriovenous fistula involving the uterine or ovarian blood vessels. Additional findings of diagnostic value were: more rapid filling and emptying of arteries running to the fistula as compared to other arteries in the pelvis, and dilatation of veins carrying blood away from the fistula.

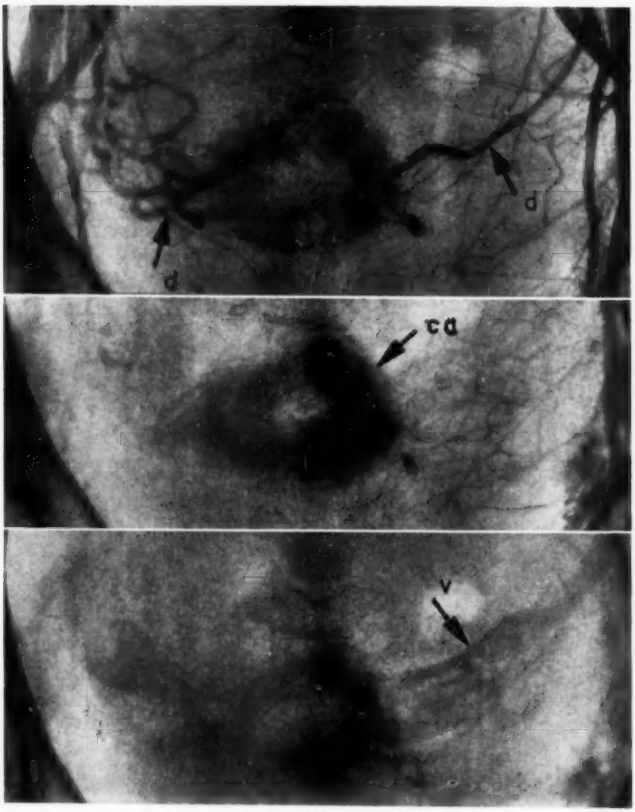

Fig. 1. Arteriograms in a case of chronic salpingitis. *Top:* Immediately after completion of injection of contrast medium. Uterine artery (d) in parametrium. Intramural blood vessels visible in uterus. *Middle:* Two seconds later. Outlining of uterus, particularly of left half, due to filling of small blood vessels. Capillary phase (ca) clearly shown. *Bottom:* Four seconds later. Veins (v) in parametrium.

On comparing the appearances in the cases examined by serial roentgenography with those in the cases in which only three films were obtained, it was found that the latter method was quite suitable for the investigation of arteriovenous fistulae of the uterus or adnexa for the following reasons: 1) The arterial phase was invariably shown in the first film, 2) only small arteries were filled with contrast medium in the second, and 3) no arteries were visible in the third.

Fig. 2. Arteriogram in a case of normal intra-uterine pregnancy of five lunar months' duration taken two seconds after completion of injection of the contrast medium. No arteries seen; placental sinuses clearly visible. Small veins (v) in uterine wall near placental attachment.

Comparison of the two methods of examination has also shown that the injection of 40 to 50 ml of contrast medium was sufficient for the demonstration of uterine or adnexal arteriovenous fistulae; this quantity does not fill the veins in the arterial phase where the circulation in the uterus or adnexa is normal.

Findings

Tables I and II show the findings in the investigation. Of the 345 cases of gynaecologic disease in this series, veins were demonstrated in 2 cases only. It is interesting to note that the veins were filled at the end of the capillary phase (Fig. 1). In the obstetric cases, however, veins were frequently visible, *i. e.* in 25 per cent.

The number of cases in which veins were visible, varied in the different groups of pregnancy, being smallest in the group of normal intra-uterine pregnancy (16 per cent). In the majority of cases in the latter group small veins in the uterine wall near the site of attachment of the placenta were filled with contrast medium when arteries were no longer visible (Figs. 2, 3).

Of the cases of ectopic pregnancy or miscarriage, veins filled in about a third. Not infrequently were they filled towards the end of the arterial phase (Figs. 4, 5). In 3 cases of ectopic pregnancy, however, they were

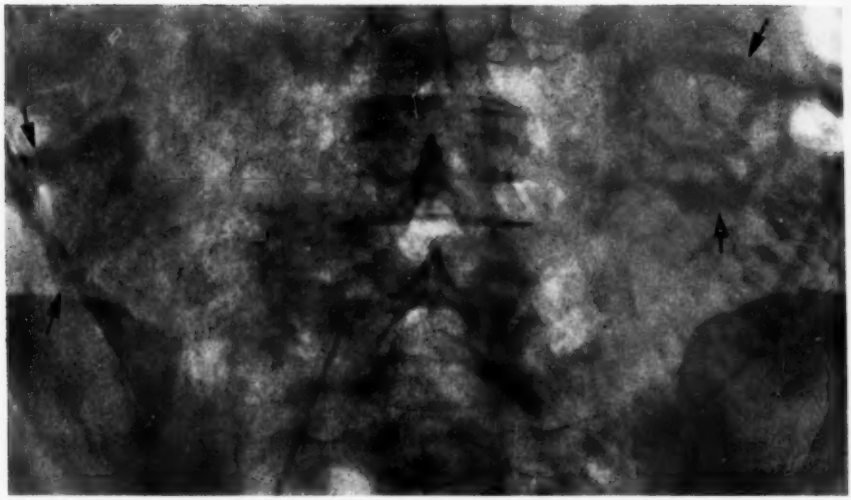

Fig. 3 Arteriogram in a case of normal intra-uterine pregnancy of seven lunar months' duration taken four seconds after completion of injection of the contrast medium. Placental sinuses, but no arteries, visible. Remarkably large number of small veins (arrows) in uterine wall.

visible early in the arterial phase, suggesting the presence of a large arteriovenous fistula (Figs. 6, 7).

Veins were also contrast filled in the arterial phase in cases of placental tumour. In 1 case of chorionepithelioma they were visible early in this phase.

The 4 cases in this series in which veins were filled early in the arterial phase were considered to be particularly interesting, both clinically and roentgenologically. They are therefore discussed in greater detail.

Case reports

Case 1. Tubal pregnancy on the right side. The patient, aged 32 years, 1-gravida, gave a history of blood-stained vaginal discharge associated with dull pain in the right lower abdomen which had persisted for two months. At times the pain increased in severity and of late she had experienced sudden intense pain daily. She therefore sought medical advice. Gynaecologic examination showed the uterus to be normal in size, no swelling being felt to the right of the corpus uteri. At *pelvic arteriography*, the right ovarian artery was filled (Fig. 6) and was remarkably wide. Early in the arterial phase the contrast medium was seen to pass from the tubal branch into the adnexal veins; all these were also wide. The diagnosis of arteriovenous fistula involving the adnexal blood vessels was

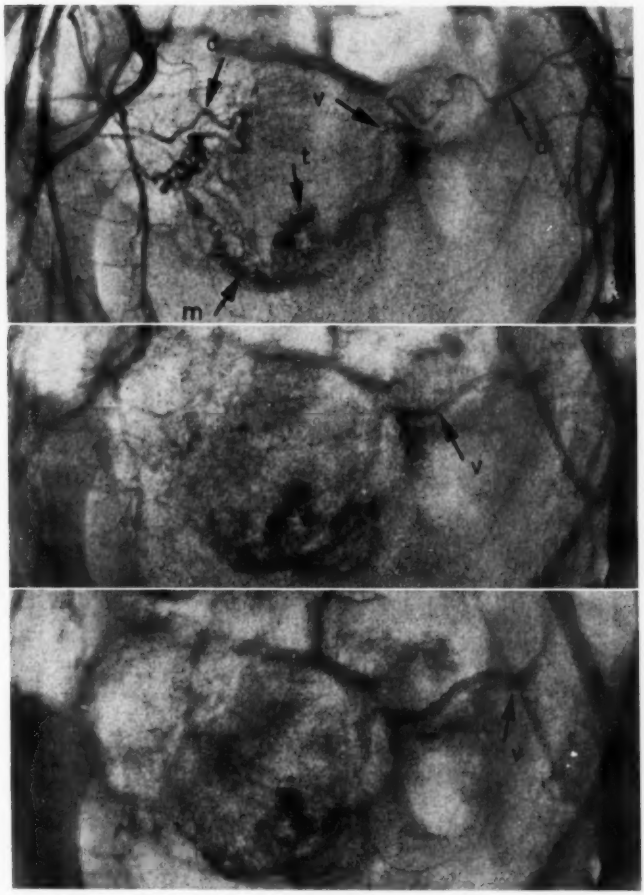

Fig. 4. Arteriograms in a case of incomplete abortion in second lunar month of pregnancy.

Top: One second after completion of injection of contrast medium. Uterine artery (d) in parametrium; fundal artery (m) carrying contrast medium to small cavities (t) representing placental sinuses from which the medium is seen to pass directly into a vein (v).

Middle: One second later. Fundal arteries and placental sinuses still visible. Efferent vein now more distinctly outlined and seen running in the parametrium.

Bottom: Two seconds later. Efferent vein (v) now clearly visible and as far as the pelvic wall.

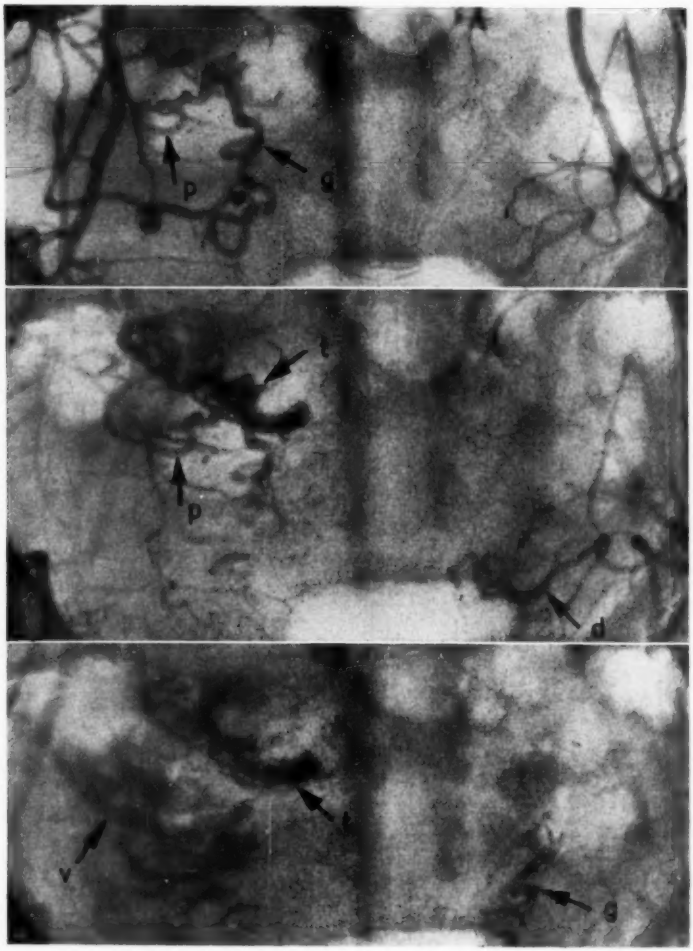

Fig. 5. Arteriograms in a case of tubal pregnancy on the right side.

Top: Immediately after completion of injection of contrast medium. Right uterine artery (g) along lateral margin of uterus; right tubal branch (p) is wide.

Middle: One second later. Left uterine artery (d) in parametrium. Right tubal branch (p) still visible; it is seen to carry contrast medium to the placental sinuses (t).

Bottom: Two seconds later. Veins (v) now visible in the adnexa and parametrium; they are seen to drain placental sinuses (t). Left uterine artery (g) runs along lateral margin of uterus.

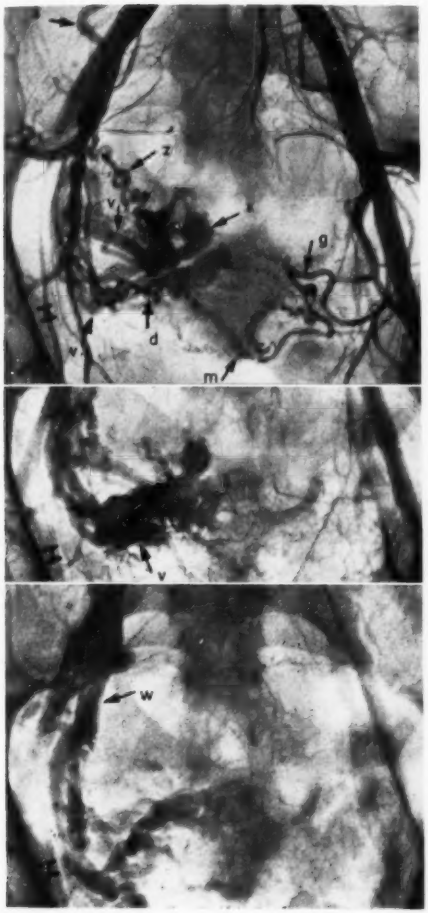

Fig. 6. Arteriograms in a case of right tubal pregnancy (Case 1).

Top view: Immediately after completion of injection of contrast medium. Right uterine artery (d) in parametrium, left uterine artery (g) runs along lateral margin of uterus. Several intramural blood vessels in uterus. Fundal branch marked (m). Right tube and ovary supplied by right ovarian artery (s) which gives off a wide tubal branch (z) running to an arteriovenous communication (x) from which the contrast medium passes into wide veins (v).

Middle view: Two seconds later. Numerous small arteries still visible in true pelvis. Large number of veins (v) seen in parametrium and pelvic wall.

Bottom view: Four seconds later. Veins in parametrium now less clearly seen. Internal iliac vein (w) and vena iliaca communis distinctly outlined.

made. *Laparotomy* disclosed a pulsating swelling, the size of a walnut, within the lateral part of the right tube. Tortuous and pulsating blood vessels over the surface of the swelling, and wide veins were identified in the mesovarium and mesosalpinx. Salpingo-oophorectomy was carried out on the right side. The operation resulted in relief from pain. Pathologic report: Tubal pregnancy and necrotic villi, some showing fibrosis.

Case 2. Interstitial pregnancy. The patient, aged 26 years, 5-gravida, underwent left salpingo-oophorectomy for an ovarian cyst in 1954. The present pregnancy was diagnosed in August 1955. The uterus did not enlarge normally and remained the size of a goose's egg, suggesting a missed abortion. Several pregnancy tests were negative. From December 1955 she had often experienced intense pain in the left lower abdomen. Later a tender and soft swelling about the size of a mandarin, arising from the left cornu,

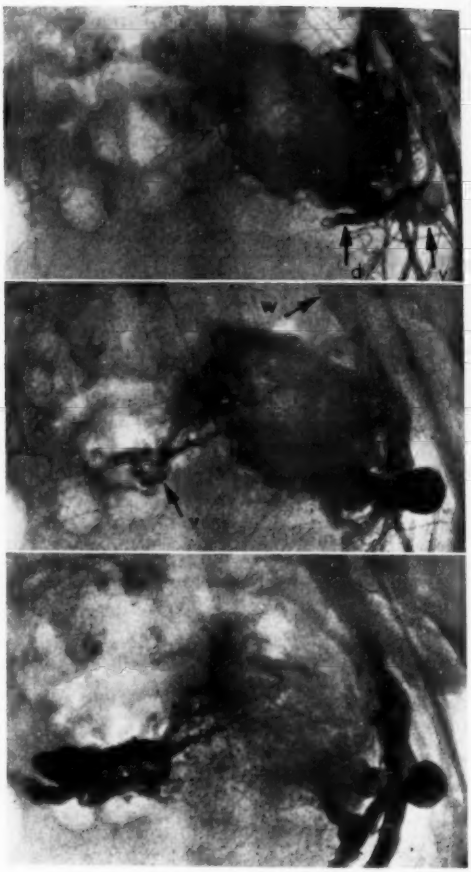

Fig. 7. Arteriograms taken in a case of interstitial pregnancy (Case 2).

Top view: Immediately after completion of injection of contrast medium. Uterine artery (d) in parametrium near isthmus. Majority of arteries in left cornu concealed by wide veins. Wide uterine vein (v) in parametrium near pelvic wall.

Middle view: Two seconds later. Small arteries and numerous intramural veins still visible within uterus. Veins (v) in parametrium on right side beginning to fill. Veins visible in parametrium and along pelvic wall on left side. Internal iliac veins marked (w).

Bottom view: Four seconds later. The intramural veins now less distinctly outlined but veins in both parametria still clearly visible.

was palpated. As the pain persisted *pelvic arteriography* was carried out in March 1956 (Fig. 7). Wide veins were visible in the parametrium in the arterial phase, as a sign of an arteriovenous fistula. It was decided to keep the patient under observation. Further pelvic arteriography carried out seven weeks after the first did not confirm the previous findings. Pain persisted but it was less severe than prior to the first pelvic arteriography; the swelling in the left cornu was found to have decreased to the size of a walnut. *Laparotomy* disclosed a dark brown and soft swelling of this size in the left cornu. The major part of the swelling was situated in the myometrium and did not extend into the uterine cavity. The mass was removed. The operation resulted in relief from pain. Pathologic report: Remains of placenta in the interstitial part of the left tube; fibrotic villi.

Case 3. Abdominal pregnancy. The patient, aged 39 years, 3-gravida, experienced sudden intense pain in the right iliac fossa which persisted for a few days and then decreased in severity. During the following weeks occasional attacks of sudden slight pain occurred. The pain suddenly increased in severity and she was admitted to hospital. At the gynaecologic examination a diffuse and extremely tender swelling, the size of a goose's egg, was palpated to the right of the corpus uteri which was found to be normal in size. *Pelvic arteriography* disclosed wide veins early in the arterial phase which proved the presence of an arterio-venous fistula. The veins were seen to run near the right lateral pelvic wall and close to the uterine artery. It was not possible to determine with certainty which artery supplied these veins but the appearances suggested that it was the uterine artery. *Laparotomy* disclosed an ovum fixed to the posterior layer of the broad ligament and the right ovary. It was found to contain a four millimeter foetus. Operation resulted in relief from pain. Pathologic report: Fibrotic villi.

Case 4. Chorionepithelioma. The patient, aged 24 years, 3-gravida, had a severe haemorrhage in the third lunar month of pregnancy. As the uterus was much larger than corresponded to the stage of the pregnancy, hydatidiform mole was suspected to be the cause of the haemorrhage. *Pelvic arteriography* was carried out (Fig. 8). Apart from veins in the uterine wall, near the site of placental attachment, wide efferent veins running along the lateral margin of the uterus filled with contrast medium after the arteries were no longer visible. The appearances substantiated the diagnosis of hydatidiform mole. As haemorrhage continued and the cervix did not open, caesarean section was performed. A mole involving the myometrium of the posterior uterine wall, occupied the uterine cavity.

Two months after the operation there was metrorrhagia on several occasions and the pregnancy test was positive. At the *gynaecologic examination* the uterus was felt to be the size of a goose's egg and a portion of the posterior wall was soft to the touch. Pelvic arteriography was again carried out and disclosed a hypervascular area within the uterine wall (Fig. 9). The drainage veins in this area were contrast filled in the arterial phase. The patient was subjected to hysterectomy which revealed a blueish-red, soft tumour the size of a hazelnut, surrounded by myometrium and situated in the posterior uterine wall. Pathologic report: Chorionepithelioma.

Discussion

As already mentioned contrast filling of veins in the arterial phase was considered to be diagnostic of arteriovenous fistula. In 4 cases in this series veins were visible early in this phase which was evidence of the presence of an abnormal arteriovenous communication (Figs. 6, 7, 9).

In 14 cases, veins were contrast filled late in the arterial phase, indicating that blood was shunted from artery to vein at a less rapid rate (Figs. 4, 5) than in the 4 cases just discussed. In some of these 14 cases the uterine artery supplying the outlined veins filled quicker than the other pelvic arteries (Fig. 5). This was further evidence in support of the diagnosis. In 13 cases in this group there was miscarriage, missed abortion, or ectopic pregnancy. It may reasonably be assumed that the necrosis of villi accounted for the establishment of the fistulous circuit, resulting in blood shunted from artery to vein.

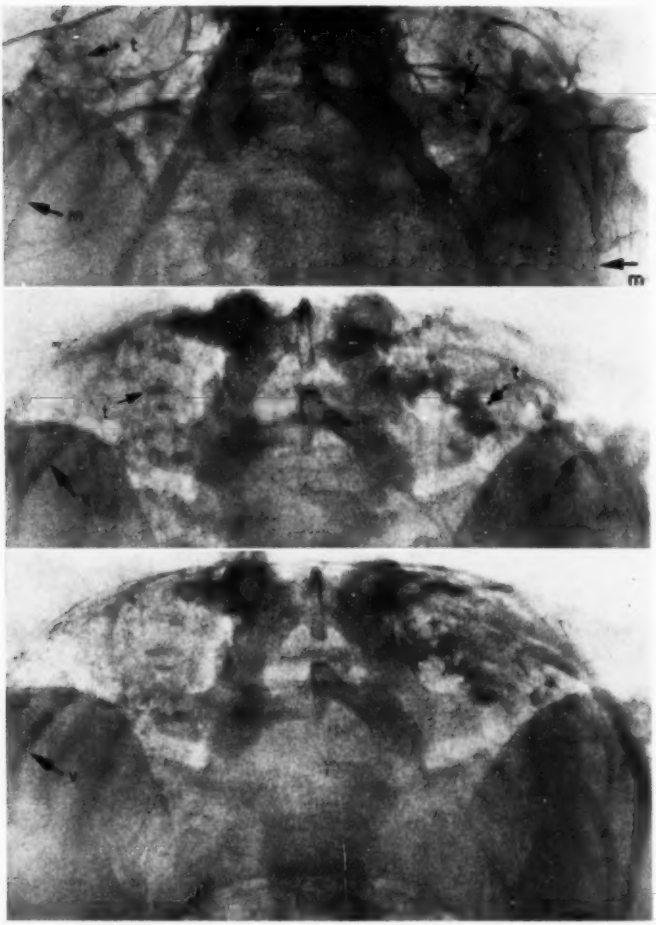

Fig. 8. Arteriograms in a case of hydatidiform mole (Case 4).

Top: Immediately after completion of injection of contrast medium. Wide intramural blood vessels (m) carry contrast material to placental sinuses (some indicated by t).

Middle: Two seconds later. Placental sinuses still visible (some indicated by t). Wide intramural veins (v) beginning to fill.

Bottom: Four seconds later. Placental sinuses now less clearly visible. Wide uterine veins (v) along lateral margin of uterus.

The remaining case in this group was of particular interest because it was the only one among 112 cases of normal intra-uterine pregnancy in which veins were visible in the arterial phase. Necrosis of villi in that portion of the placenta in which veins were visible may have accounted for the abnormal arteriovenous communication in this case.

Of the 345 cases of gynaecologic disease veins filled in only 2 cases, and then after the arterial phase (Fig. 1). As demonstration of veins after the arterial phase is no criterion of the presence of an abnormal arteriovenous communication such a condition could reasonably be excluded in these 2 cases.

In 25 cases of pregnant women veins were filled with contrast medium after the arterial phase (Cf. Table II). The presence of an abnormal arteriovenous anastomosis could therefore be excluded.

The findings in this investigation did not support the view that the normal placenta represents a modified arteriovenous fistula for the following reasons. One was that of the 112 cases of normal pregnancy no veins were filled with contrast medium in 94. Another reason was that of the remaining 18 cases veins were visible after the arterial phase in 17.

However, the following sources of error must be considered in interpreting arteriograms in cases of normal pregnancy: 1) Due to the increased blood supply of the pregnant uterus the contrast medium is diluted in the uterine arteries to a greater extent than in the non-pregnant uterus, its concentration in the veins being therefore probably too weak to render them visible; 2) sedimentation of the contrast medium owing to the slow circulation in the placental sinuses. This was clearly shown in several arteriograms. Probably only those efferent veins which carry blood away from well-filled parts of the placental sinuses are visible whilst those draining non-filled or only fragmentarily filled parts are invisible.

The principal factor concerned in the origin of the abnormal arteriovenous communication in the cases of ectopic pregnancy, miscarriage, missed abortion, and hydatidiform mole was probably necrosis of villi, blood being thereby shunted from artery to vein without being checked by the villi. In the case of chorionepithelioma the malignant trophoblastic cells probably also injured the walls of an artery and vein resulting in an arteriovenous fistula.

It has hitherto not been known that necrosis of villi can give rise to an arteriovenous fistula, the consensus of opinion being that the origin of the lesion is congenital, traumatic, or that it results from a tumour.

A necrotic placenta with an arteriovenous fistula produces symptoms in the form of pain which disappear after removal of the placenta. The diagnosis of the lesion may be difficult. Pelvic arteriography proved to be of diagnostic value in these cases.

Fig. 9. Arteriograms in Case 4, two months after those in fig. 8. Two months following operation for hydatidiform mole, chorionepithelioma was diagnosed. *Top:* Immediately after completion of injection of contrast medium. Uterine artery (g) along lateral margin of uterus. Numerous intramural blood vessels shown within the uterus, some being seen to run towards a hypervascular area (x). At operation a chorionepithelioma, the size of a hazel-nut, was found within this area. Veins (v) in vicinity of this area. *Middle:* Two seconds later. Small intramural arteries still visible. Numerous intramural veins seen. Veins in the parametrium beginning to fill. *Bottom:* Four seconds later. Intramural veins now less distinctly outlined. Veins in parametrium clearly visible.

In contrast to congenital or traumatic arteriovenous fistulae, those resulting from necrosis of villi may apparently close spontaneously. This was illustrated by the case of interstitial pregnancy (Case 2) in which pelvic arteriography was carried out on two occasions, the appearances at the first examination being diagnostic of an abnormal arteriovenous communication whilst no evidence of this was found at the second examination.

It is difficult to assess the incidence of arteriovenous fistula resulting from ectopic pregnancy. The lesion appears to be of not infrequent occurrence but it is generally not recognized for the following reasons. One is that it produces atypical symptoms; another reason is that the arteriovenous fistula within the tumour escapes attention where laparotomy is carried out.

In a previous paper on the value of pelvic arteriography in the diagnosis of hydatidiform mole and chorionepithelioma (BORELL et coll. 1955) the appearances suggested the presence of a pathologic arteriovenous communication. This led the authors to assume that the lesion might be diagnostic of a placental tumour. The present investigation has shown that also miscarriage, missed abortion, and ectopic pregnancy may give rise to arteriovenous fistula.

SUMMARY

Pelvic arteriography was carried out in a material of 517 cases; veins were filled in 45 cases and these form the basis of the investigation. It is shown that miscarriage, missed abortion and ectopic pregnancy may give rise to arteriovenous fistulae of the uterus or adnexa. In contrast to congenital and traumatic arteriovenous fistulae those resulting from ectopic pregnancy may apparently close spontaneously. The findings in the investigation did not support the view that the normal placenta represents a modified arteriovenous fistula.

ZUSAMMENFASSUNG

Beckenarteriographien sind in einem Material von 517 Fällen ausgeführt worden. Die Venen waren in 45 Fällen gefüllt und diese bilden den Ausgangspunkt der Untersuchung. Es hat sich gezeigt, dass Fehlgeburten, verhaltene Aborte und Extrauterinschwangerschaften zu arterio-venösen Fisteln des Uterus oder der Adnexe Anlass geben können. Im Gegensatz zu kongenitalen oder traumatischen arterio-venösen Fisteln können sich solche, die durch Extrauteringraviditäten entstanden sind, wahrscheinlich spontan schliessen. Die Befunde in dieser Untersuchung geben keinen Anhalt für die Auffassung, dass die normale Plazenta eine modifizierte arterio-venöse Fistel darstellt.

RÉSUMÉ

Une artériographie pelvienne a été pratiquée dans 517 cas; les veines ont été visualisées dans 45 cas; ceci est à la base de ce travail. Ces recherches ont montré que l'avortement, la menace d'avortement et la grossesse extra-utérine peuvent donner lieu à des fistules artério-veineuses de l'utérus ou des annexes. A la différence des fistules artério-veineuses congénitales et traumatiques, celles qui proviennent d'une grossesse extra-utérine semblent pouvoir se fermer spontanément. Les résultats de ces recherches n'ont pas confirmé l'opinion que le placenta normal représente une fistule artério-veineuse modifiée.

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A METHOD OF SIALOGRAPHY

by

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Sialography was introduced simultaneously and independently by BARSONY (1925), USLENGHI (1925) and CARLSTEN (1926), a contrast medium of high viscosity being used (Lipiodol or iodized oil). For current methods water-soluble contrast media are unsuitable as they tend to be washed out from the ducts by the saliva flow before a sufficient number of exposures has been obtained unless the syringe is left in position throughout the procedure.

The contrast medium has generally been injected through a blunt-ended cannula introduced into the main salivary duct. As the exposures must be made almost simultaneously with the injection, the hands of the investigator are apt to receive undue doses of radiation. Some operators have introduced a fine catheter in the main duct in order to obtain better protection. CARLSTEN used a ureteral catheter and RUBIN a polythene tube. STEINHARDT (1942) secured the catheter with a suture in some cases in order to avoid back-flow of the contrast medium into the oral cavity.

It is generally accepted that the contrast medium should be injected until the patient experiences a distinct feeling of tension in the gland; as a rule, 0.5 to 2.0 ml are needed (ZUPPINGER 1951).

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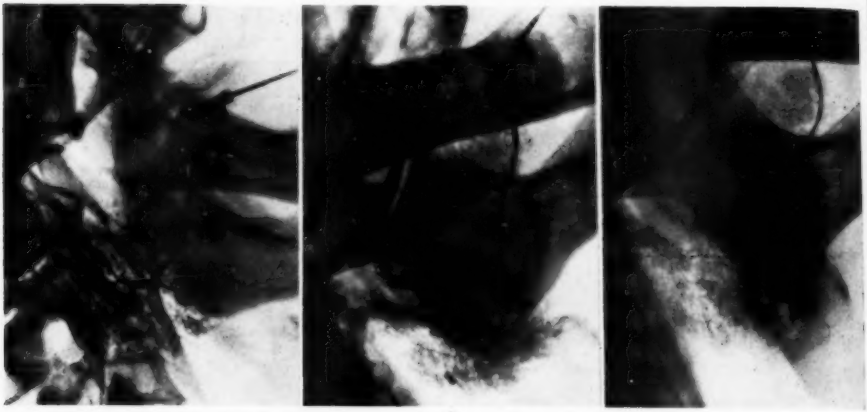


a b c

Fig. 1. Ordinary sialography after direct injection of viscous contrast medium. a) Dionosil. Extensive parenchymatous filling with blurring of the intraglandular ducts. b) Lipiodol. Diffuse parenchymatous filling, droplets of contrast medium in the mouth. c) 20 minutes later. The salivary flow arrested by plugging of ducts with the oily medium. Considerable swelling of the parotids following these examinations.

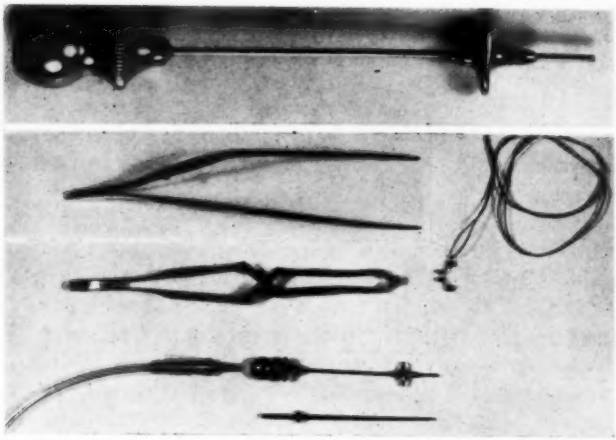
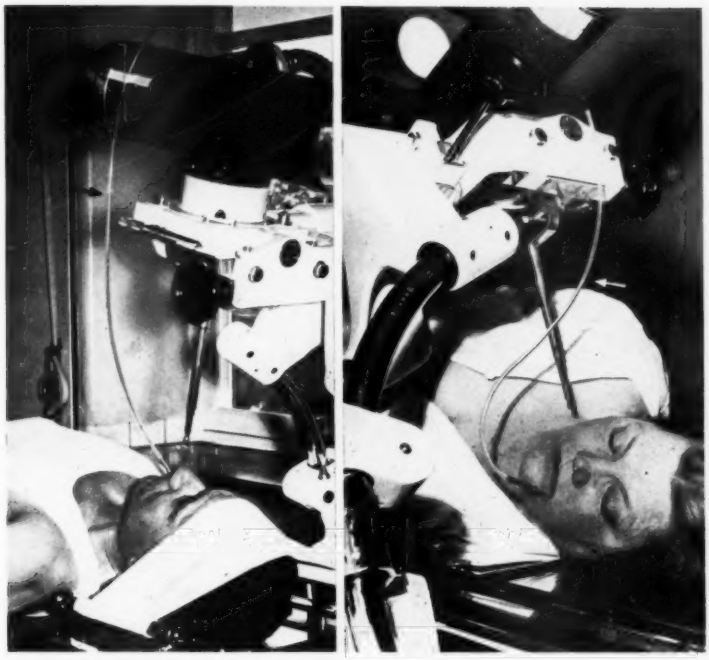


Fig. 2. Special cannula and other instruments needed for sialography.



a b

Fig. 3. Positioning for a. p. and lateral views of parotid ducts. Level (→) of contrast medium in plastic tube (a). Sewing thread tied to clip, so that the latter cannot escape in the mouth if it is dropped or slips away (b).

In several cases examined by the present authors with these methods heavy contrast-filling of the parenchyma resulted (Fig. 1). When such a parenchymatous filling occurred, the patient complained of severe pain and swelling of the gland. We have found that the small ducts become plugged (Fig. 1b) and the outflow of the saliva is seriously impaired for a considerable time (Fig. 1c) by the injection of an oily contrast medium. Considerable swelling of the gland occurs and is evidently the result of salival obstruction, since the injection of 1 ml of contrast medium could not give rise to such an increase in the volume of the gland.

The following method eliminates leakage into the oral cavity, and at the same time parenchymatous filling of the gland as well as impairment of its function is avoided.

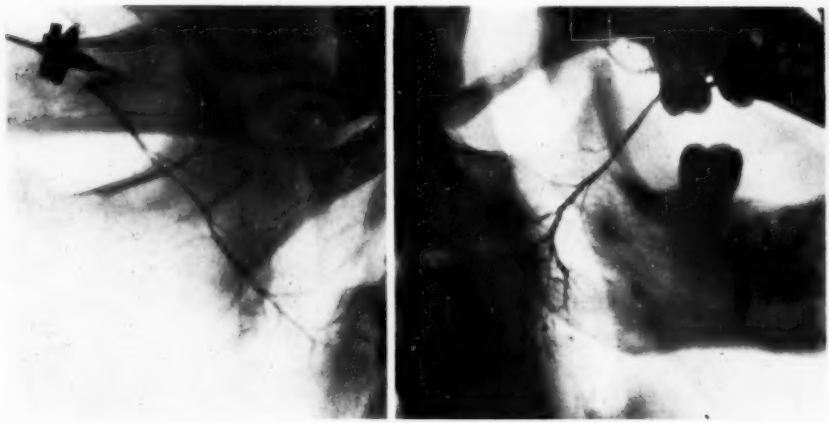


Fig. 4. Normal parotid ducts. Urografin 60 %. No parenchymatous filling obtained.

Material and technique

The parotid gland as well as the submaxillary gland on the same side were investigated in a material of 40 cases.

The shape of the cannula and the other instruments required are depicted in Fig. 2. For probing, and slight dilatation of the oral end of the duct, a lachrymal canal probe of silver, which is pointed but not sharp, should be used.

The location of Stensen's duct usually offers no difficulties, the orifice being found opposite the second praemolar or first molar tooth. Stimulation of the flow of saliva with lemon juice is unnecessary; the probe is held ready in the one hand and the gland compressed so as to cause a flow of saliva from the orifice of the duct. The orifice of the submaxillary duct is more easily found if the caruncle is held with nontraumatic forceps (see Fig. 2). When the cannula has been introduced, a clip is placed around the cannula and secured to the buccal mucosa (or in the frenulum under the tongue, depending upon the gland to be examined). When introducing the cannula into the submaxillary duct, a finger should be placed under the patient's chin and the floor of the mouth pressed upwards in order to facilitate the securing of the clip onto the frenulum. Patients seem to experience surprisingly little discomfort from the procedure and only at the moment of securing the clip may momentary sharp pain be felt. No form of anaesthesia is employed. When the cannula has been fixed in position, saliva will

a b c

Fig. 5. Normal submaxillary ducts. Wharton's duct is normally wider than Stensen's duct. c) True a. p. view of same case as in (b).

Fig. 6. Large mixed salivary gland tumour in middle part of parotid gland. True a. p. view.

Fig. 7 a

Fig. 7 b

Fig. 7. Man, aged 30, with advanced sicca (Sjögren's) syndrome. a) Left parotid with large cavities in posterior part and globular dilatations in remainder of gland. b) Right parotid with punctate and globular dilatations of ducts characteristic of the disease when moderately developed.

Fig. 8

Fig. 8. Cicatricial stenosis of orifice of Stensen's duct. In such cases the dilatations of the main duct with normal intraglandular ducts are common.

usually flow through it spontaneously, if not, the gland should again be palpated until saliva emerges and the cannula is clear from air bubbles. A polythene tube filled with a water-soluble contrast medium of high concentration (Urografin or Hypaque, 60 % or more), and also free from any air bubbles, is attached to the cannula. The other end is raised. The flow of contrast medium occurs as an effect of ordinary hydrostatic pressure (about 30 to 40 cm H_2O). The cannula is apt to stay in close contact with the wall of the duct and thus create an obstacle to the passage of the contrast medium; this may be eliminated if slight traction is exerted on the cannula or the corner of the mouth (in case of a parotid gland examination). Furthermore, by carefully changing the position of the cannula in the duct, the flow of the medium can be controlled or interrupted. When about 1 ml of medium has been introduced, the speed of the inflow diminishes and the patient experiences a slight sensation of fullness in the gland. The exposures are then made. True a. p. projections should always be obtained in order to evaluate any displacement of the ducts (Figs. 3, 5c, 6). A satisfactory view of the posterior parotid ducts is obtained if the chin is tilted about 15° upwards in the lateral projection (Fig. 3b).

Results

Optimal filling of the parotid and submaxillary ducts was always obtained with this method. The pressure used for the injection is only slightly higher than the secretory pressure. Parenchymatous filling with 'blurring' never occurs, which is of particular importance in the diagnosis of early cases of the sicca (SJÖGREN's) syndrome (Fig. 7). The small punctuate ectasias characteristic of this condition are easily overdistended and burst if the injection is made with a syringe.

The cannula is available from G. CRONA, Instrument maker, Lasarettet, Lund, Sweden, or from KIFA, Solna 3, Stockholm, Sweden.

SUMMARY

A method of sialography by which a water-soluble contrast medium is injected without leakage into the mouth is described. Optimal filling of the ducts is obtained without the risk of overdistension, swelling of the glands, or pain.

ZUSAMMENFASSUNG

Eine Sialographiemethode wird beschrieben bei der man ein wasserlösliches Kontrastmittel injiziert ohne Läckage in die Mundhöhle. Optimale Füllung der Gänge wird dabei ohne das Risiko einer Überdehnung, einer Anschwellung der Drüsen oder von Schmerzen erreicht.

RÉSUMÉ

Description d'une méthode de sialographie par injection d'un moyen de contraste hydrosoluble sans suintement dans la bouche. On obtient un remplissage optimum des canaux sans risque de distension excessive, de gonflement des glandes ni de douleur.

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FROM ROENTGENDIAGNOSTIC DEPARTMENT I (DIRECTOR: DOCENT G. JÖNSSON), SÖDERSJUKHUSET, STOCKHOLM, SWEDEN

EXPERIMENTS WITH CHOLECYSTOKININ IN CHOLECYSTOGRAPHY

by

Bror Brodén

Contraction of the gallbladder and enzyme secretion from the pancreas may by caused by substances extracted from the mucous membrane of the uppermost part of the small intestine. The gallbladder contracting factor in extracts from the intestines was discovered by IVY and GOLDBERG in 1928. They named it cholecystokinin. In 1943, HARPER and RAPER found that the mucous membrane of the intestine contained another hormone, called pancreozymin, which has no secretion effect but stimulates an enzyme secretion from the pancreas. As early as 1930 cholecystokinin was tentatively injected in human subjects by IVY, DREWYER and ORDNOFF. The attempt was repeated in 1947 by IVY and in 1949 by DENTON, GERSHBEIN and IVY. In England, DUNCAN et coll. (1952) suggested the use of pancreozymin preparations with cholecystokinin activity for the study of gallbladder contractions in connection with the ordinary secretin test. As late as 1955, IVY showed films demonstrating the action of cholecystokinin in man.

In spite of all these attempts, no series of clinical investigations have so far been performed, as far I am aware, with cholecystokinin.

Submitted for publication 12 September 1957.

In 1955, JORPES and MUTT of Chemistry Department II of Karolinska Institutet in Stockholm supplied us with a cholecystokinin preparation to be tried out in cholecystographies. Two or three milligrams of this preparation were assumed to be a sufficient dose in man. The experiments were conducted in normal subjects as well as in a clinical material of 61 cases. The possibilities of filling the bile ducts with contrast medium were first investigated. The results were reported at clinical meetings at Karolinska Sjukhuset, in 1955 and in 1956, and they will be briefly summarized below.

In normal cases, contraction of the gallbladder, contrast filling of the choledochus, and passage of contrast medium into the duodenum were obtained. The contraction of the gallbladder began during the first few minutes after the injection of cholecystokinin, and lasted for a maximum of 20 minutes. In some of the cases, partial retrograde contrast filling of the hepatic duct was observed. Attempts to produce or increase this retrograde filling of the hepatic duct with morphia failed.

Contraction of the bladder and contrast filling of the ducts were also obtained after the injection of cholecystokinin in cases with gallbladder concretions. In none of these cases could choledochus concretions be demonstrated; such concretions are rare in cases with a normally functioning gallbladder. In some of the cases, emptying of the gallbladder was delayed by a stone impacted in the neck. In one case, emptying was prevented by calculus in the cystic duct.

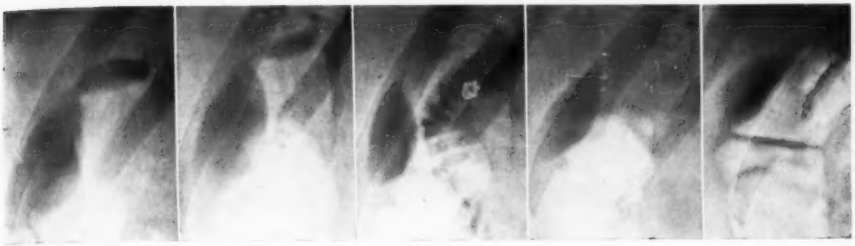
Following this investigation, an additional 29 normal cases have been examined, particular attention being paid to the emptying of the gallbladder. All the subjects were adults without abdominal symptoms and with normal findings at cholecystography. Seven were 31 to 56 years of age and with diseases which are irrelevant in the present connection, and the other 22 were students.

Method

Cholecystography was performed by the standard method, the contrast medium being Telepaque (iodopanoic acid). During the cholecystokinin experiment the patient was placed in an oblique supine posture with the right side down, this position being carefully maintained during the entire investigation.

The beam direction was vertical. A series of films were obtained between one and 30 minutes after the injection of cholecystokinin. In the early experiments, one film per minute was taken during the first 10 minutes, and then one every second minute for the following 20 minutes. Later on the number of films was decreased. The series were always continued until at least 20 minutes after the injection.

The cholecystokinin was dissolved in physiologic saline solution to a concentration of 1 mg/10 ml. In three cases, in which the preparation was introduced by infusion, the concentration was lower (1 mg/33 or 67 ml).



a b c d e

Fig. 1. Contraction of the gallbladder in a normal case. a) Before the injection of cholecystokinin. b), c), d), and e): 1, 4, 10 and 30 min, respectively, after the injection.

Contractions of the gallbladder

Contraction of the gallbladder is associated with an increase in pressure. This exerts a straightening influence upon the gallbladder and the cystic duct, which while at rest form a more or less curved system. As a result the position of the gallbladder is changed, to an extent differing greatly from case to case and depending upon variations in individual bodily characteristics. During the contraction the gallbladder also changes shape.

These changes in position and shape make it impossible to determine, by measurements on the films, the volume decrease of the gallbladder for a given time interval during the contraction. This has not even been possible when films were taken in two planes perpendicular to each other.

A rough measurement of the contraction may be obtained, however, by measuring the largest transverse diameter of the gallbladder, and this is the method we have employed.

The contraction of the gallbladder has usually started as early as one minute after the injection and has mostly taken place within the first ten minutes. It has generally not lasted more than 20 minutes, although occasionally 30 minutes, after the injection of cholecystokinin. The diameter has therefore as a rule been measured no earlier than the 30-minute film. In some cases this was not possible as the contrast medium had become so diluted with bile that the contour of the gallbladder could no longer be seen. In such cases the measurement was made in the 20-minute film. In 5 cases, in which the injection was repeated, measurements were obtained 20 minutes after each injection.

The contractions of the gallbladder have been classified in the following manner. If the diameter decreased to less than two-thirds of the

diameter prior to the injection, the contraction was termed considerable. If the diameter decreased by 2 mm or less, it was considered that no contraction had occurred.

Two different preparations produced by JORPES and MUTT have been used. They are identified below as preparations II and III.

In the experiments, the following variables were introduced: 1) Two different cholecystokinin preparations; 2) The amount of cholecystokinin injected; 3) The injection rate.

Results

Contraction of the gallbladder was observed in 26 out of 29 cases, in 10 of which it was considerable.

In the remaining three cases no contraction was noted.

A. Comparison between the effect of preparations II and III. With preparation II considerable contraction was obtained in 4 out of 17 cases. For preparation III the corresponding figures were 2 out of 12. In all three cases in which there was no contraction, preparation II had been used.

B. Comparison between the amount of the preparation and the degree of contraction. The amount of cholecystokinin varied between 1 and 12 mg. Considerable contraction was obtained in one case with 2 mg (injection rate 6 mg/min). In two cases only moderate contraction was obtained with 12 mg (1.5 to 1.6 mg/min). In the three cases with no contraction, 3 and 6 and 6 mg were used (6, 12 and 6 mg/min respectively).

C. Comparison between the amount of preparation injected per minute and the degree of contraction. Considerable contraction was obtained in one case with as low an injection rate as 0.2 mg/min (7 mg cholecystokinin). In three cases with an injection rate of 15 mg/min (1 mg), moderate contraction was obtained. In the three cases without contraction the injection rates were 6, and 12 and 6 mg/min.

D. Repeated injections of cholecystokinin. In 5 cases the injection of cholecystokinin was repeated immediately after the contraction was completed. These cases are also included under (B) and (C) above.

In three of the cases, 3 + 3 mg were injected with an interval of 20 minutes. In one of these there was no contraction, and in the two others contraction was observed following each injection of cholecystokinin.

In the two remaining cases of repeat injections, 1 + 2 + 3 mg were

injected with an interval of 20 minutes, resulting in one case in definite contraction after the first and third injections, in the other after the second and third injections.

Reactions

No severe secondary reactions have been observed with the two preparations. In 7 cases, there were slight secondary reactions. These consisted of a sensation of heat in the face or facial blush (2 cases), general sensation of warmth (4 cases) and pain in the gallbladder region (1 case). These symptoms have been produced by both preparations — by preparation II in 4 out of 17 cases and by preparation III in 3 out of 12 cases. There has been no definite indication of a relationship between the secondary reactions and the amount of the preparation and the injection speed, considered separately, but reactions seem to occur when a comparatively large amount of cholecystokinin is injected rapidly. In 3 cases, 1 mg was injected at a rate of 15 mg/min and in 2 cases 12 mg at a rate of 1.5 to 1.6 mg/min. None of these five cases had any secondary reactions. In 3 cases, 6 mg was injected at a rate of 12 mg/min; all these 3 cases had secondary reactions. In a material of 61 patients previously published by the author, there were secondary reactions only in 4 cases. In this material the amount of cholecystokinin did not exceed 8 mg, and the injection rate was not higher than 6 mg/min.

Conclusions

No difference has been observed in the degree of contraction of the gallbladder within the limits between which the amount of the preparation and the injection rate have been varied. The risk of secondary reactions seems to increase by the product of these factors.

It appears from the investigation that with the preparations used by the author only 2 to 3 mg of cholecystokinin need be injected to produce a contraction of the gallbladder. If an injection time of 20 to 30 seconds or more is used, the risk of secondary reactions is insignificant.

SUMMARY

The contraction of the gallbladder after the injection of cholecystokinin was investigated in connection with cholecystography in a material of 29 healthy adults. The contraction was independent of the amount and the injection rate of the hormone, and was effected by 2 to 3 mg of cholecystokinin. Slight secondary reaction occurred in 7 cases.

ZUSAMMENFASSUNG

Die Kontraktion der Gallenblase nach Injektion von Cholecystochinin ist bei Cholecystographien in einem Material von 29 gesunden Erwachsenen untersucht worden. Die Kontraktion war von der Menge und der Injektionsgeschwindigkeit des Hormones unabhängig; sie erfolgte nach 2 bis 3 mg Cholecystochinin. Leichte sekundäre Reaktion trat in 7 Fällen auf.

RÉSUMÉ

L'auteur a étudié la contraction de la vésicule biliaire après injection de cholécystokinine au cours de la cholécystographie sur une série de 29 adultes sains. La contraction est indépendante de la quantité et de la rapidité d'injection de l'hormone, et est modifiée par 2 à 3 mg de cholécystokinine. De légères réactions secondaires se sont produites dans 7 cas.

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FROM THE ROENTGEN DEPARTMENT (DIRECTOR: PROF. J. FRIMANN-DAHL)
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SELECTIVE ANGIOGRAPHY IN RENAL TUBERCULOSIS

by

J. Frimann-Dahl

Renal tuberculosis may be diagnosed radiologically with great certainty by a number of methods although a combination of several is usually required. Intravenous urography with sustained compression is the basic method. Retrograde pyelography is helpful in some cases; angiography gives additional information and is of great importance, especially when partial resection is planned. Aortography was first made by a translumbar approach but this procedure has now been more or less abandoned; in our department the last translumbar puncture was made in 1954. The next step was aortography, performed after percutaneous introduction of a catheter into the femoral artery, and this method is still used in many cases and has a firmly established reputation. The procedure has many advantages, as will be shown later, and above all gives a good survey of the renal vessels.

Angiographic studies may now, however, be carried a stage further by the selective injection of contrast medium through a catheter introduced into the femoral artery and advanced into the renal artery (EDHOLM & SELDINGER, ÖDMAN). Experience with this method has been published by these authors in cases of tumours, cysts, and hydronephrosis, but so far not in renal tuberculosis.

Paper read at the XXI Inter-Scandinavian Congress of Radiology, Copenhagen 1957.
Submitted for publication 5 August 1957.

Technique

We employ an opaque catheter, size 205, the end of which is curved to a slight hook. The hook is formed by dipping the extremity in hot water, moulding it to the desired angle, and then placing the catheter in cold water. The catheter is fitted with a metal leader. The catheter and the leader are introduced into the aorta by way of femoral puncture. As long as the metal leader fills the whole of the catheter, the extremity of the latter will be kept straight, but will bend again when the leader is withdrawn; this may be observed by fluoroscopy. One may also see the tip of the catheter, which slips into the renal artery quite easily, being pushed or sucked by the blood stream. The catheter should lie in a direction away from the spine. We like to be sure that the catheter does not occlude the artery completely, and this may be checked quite easily by injecting a few ml of contrast medium under fluorescent control. If the artery is occluded by the catheter, the patient may feel slight pain in the flank as the injection is made. If the catheter is correctly placed, he will feel nothing, even if 10 ml of contrast medium are injected.

For many reasons, which will be discussed later, we prefer first to carry out conventional aortography (30 ml contrast medium 50 % in one injection). This gives a general orientation especially regarding the size and number of the renal arteries. The polythene catheter employed is then replaced by an opaque catheter for the selective angiography. When everything is ready, the contrast medium, 8 ml Hypaque 35 %, is injected by hand as quickly as possible. Films are taken at short intervals, preferably with an automatic film changer and, if desired, in various oblique positions. The catheter may remain in situ until the films are examined, and a second injection may be made if necessary. The catheter is kept patent by the injection of normal saline, the pulsation of the blood column being checked before injection of the contrast medium. Following withdrawal of the catheter, the femoral artery at the puncture site is compressed for some 10 minutes to prevent hematoma formation.

As previously stated, the selective angiography offers many advantages compared to other angiographic methods. First, it is possible to direct the injection of the contrast medium into the renal artery so that no other vessels cover the field to be examined. This is most strikingly evident on the left side where the mesenteric vessels in conventional aortographies often run across the kidney and at times make an exact interpretation difficult or impossible. This may also be true of the right side although here the extrarenal vessels are usually less disturbing.

The films obtained in selective angiography are definitely of a better quality than those taken after the injection of contrast medium into the aorta. We use a cone centered over the kidney to be examined. Comparison has been made between films obtained with a film changer and a Bucky diaphragm. Films taken with a moving grid seem to be preferable to those made with the stationary grid of the film changer and show more detail. On the other hand, the films can of course be obtained in rapid sequence when a film changer is used and will thus ensure better coverage of all phases of the arterial and venous circulation.

The material is a continuation study of cases of renal tuberculosis submitted for surgical treatment, that is, in the majority of the cases to

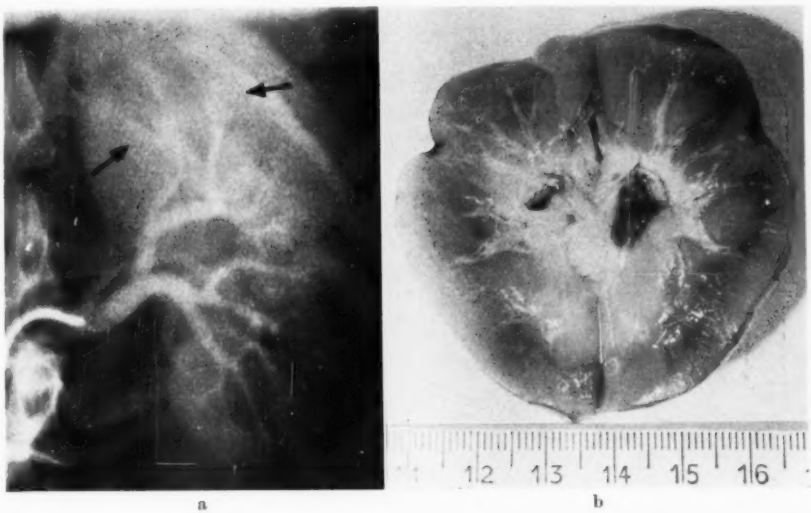

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Fig. 1. a) Selective angiography in renal tuberculosis. Cavities in left upper pole. Two arterial branches of the arteries are irregular. b) Specimen of left upper pole after segmental resection.

partial resection (SEMB, FRIMANN-DAHL). The operative series has now reached 178, and 85 of these have been examined by translumbar aortography, 48 after catheter replacement, and 17 with selective angiography. As to the diagnosis and treatment of kidney tuberculosis in general, reference is made to the abovementioned papers. In the following, only the roentgen findings will be discussed. Our experience is based on 23 cases of which some are still under observation and antibiotic treatment.

There are three important main points in the angiographic findings: 1) The course of the main vessels and their branches, 2) changes in the smaller vessels (local pathology), and 3) the nephrographic effect and defects in the parenchyma.

It has been emphasized in earlier works (WEYDE, FRIMANN-DAHL) that it is important for the surgeon to know before the partial resection the exact course of the larger vessels. This problem is in most cases better solved by selective angiography than by conventional aortography, mainly due to the fact that no other vessels disturb the field. In partial resections it is also of importance to know which vessels run anteriorly or posteriorly. This can be shown in many cases by taking films in different oblique positions. Stereo-angiography may possibly also be helpful, although as yet we have no experience in this method.

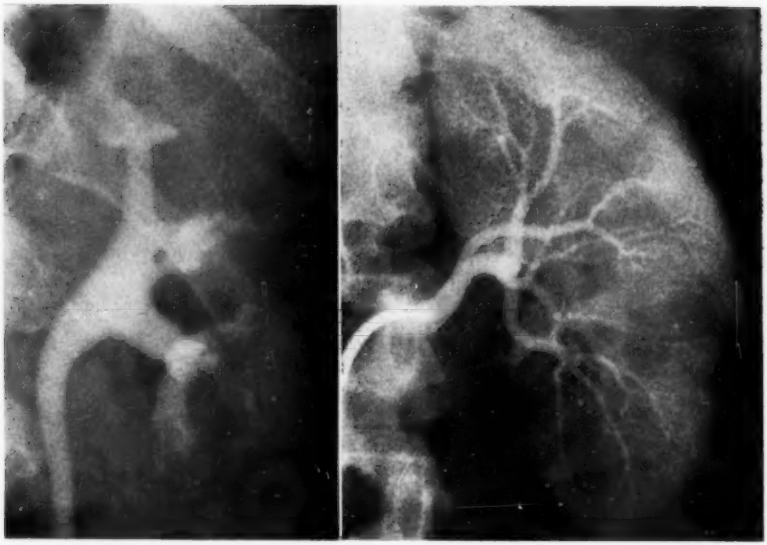

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Fig. 2. a) Urography. Papillary necrosis in middle and lower segments. Under antibiotic treatment. b) Selective renal angiography (same case). Small irregularities of vessels corresponding to the papillae. Destruction of parenchyma causing indentation of the surface of the kidney.

The local pathology varies considerably and it is hardly possible to define the changes precisely. WEYDE has described in considerable detail the aortographic appearances observed in renal tuberculosis. These may be demonstrated better and more clearly, however, by selective angiography.

When only *smaller foci* are present the vascular pattern may be practically normal or so little interfered with that any diagnosis based on the angiograms alone is impossible. The first changes seem to be small irregularities in one or more branches of the arteries (Fig. 1). They may be pushed apart, bent or curved, blocked, narrowed, or dilated (Fig. 2). These alterations may be minor ones and difficult to demonstrate without the most careful scrutiny. Comparison with the normal vessels in the remainder of the kidney (or with the vessels of the other kidney) may be helpful in detecting a lesion. A normal vascular pattern is of great assistance in ruling out pathologic changes and thereby securing a good result in partial resection, naturally of the utmost importance when the other kidney has been removed (Fig. 3).

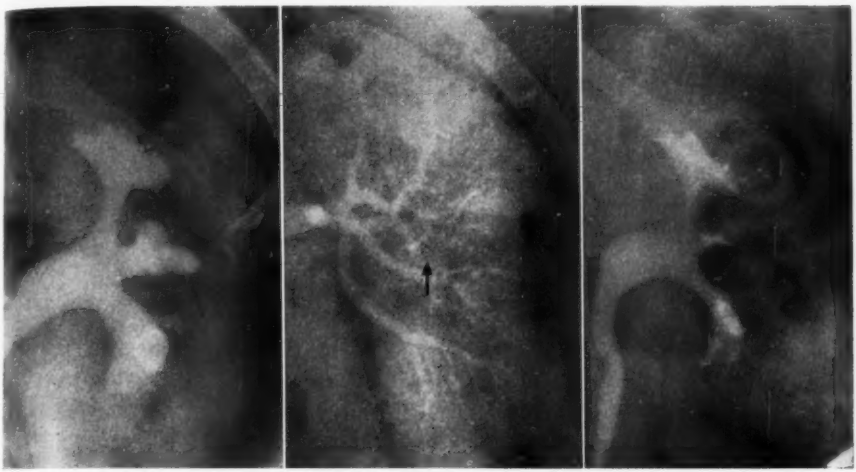

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Fig. 3.

a) Tuberculous cavity in middle lobe of one remaining kidney; defect on lateral contour.

b) Selective angiography. Tortuous, partially occluded vessels corresponding to lesion.

c) After partial resection, good function of kidney. Pelvis nearly of normal shape.

d) Resected middle segment with cavity.

When calcifications are present, these certainly make the localization easier and indicate where to look for the abnormal vessels. In this connection it should be mentioned that calcifications in the wall of a cavity suggest a smaller chance of success by antibiotic treatment, and therefore are most important as an operative indication. It should not be forgotten that the demonstration of small calcified foci demands a careful roentgenographic technique.

Indentations of the renal outline are sometimes helpful in disclosing the site and size of the focus. The defects are better shown in selective angiograms than in urograms and aortograms (Fig. 4). The exact site of the focus may also be well demonstrated by the second injection. The

Fig. 4

Fig. 5

Fig. 4. Hazelnut-sized focus in upper part of the right kidney, pushing the upper branch of the artery downwards.

Fig. 5. Selective angiography. Defect in renal contour near lower pole. Irregular vessels around a hazelnut-sized focus.

first injection thus serves to produce more or less a urography in which the calyces as well as any cavities may be filled. The second injection may then show the contrast medium in the tuberculous focus, and at the same time in the vessels surrounding the lesion (Fig. 5).

The changes in cases of *larger foci* are naturally more conspicuous. Several branches of the renal artery may be blocked completely, giving a poorly or non-vascularized zone of varying size (Fig. 6). This is most valuable in cases with calyx occlusion and no other sign of destruction in the urogram (Fig. 7).

The arteries may also be observed to run claw-like around a cavity or an abscess, and thereby outline the size of the area of destruction. In very rare instances the tuberculous foci may escape detection, even when all methods are employed. This happened, for example, in a case of a subcapsular abscess, the size of a hazel-nut, situated medially close to the hilum, in which even a postoperative revision of the films failed to disclose

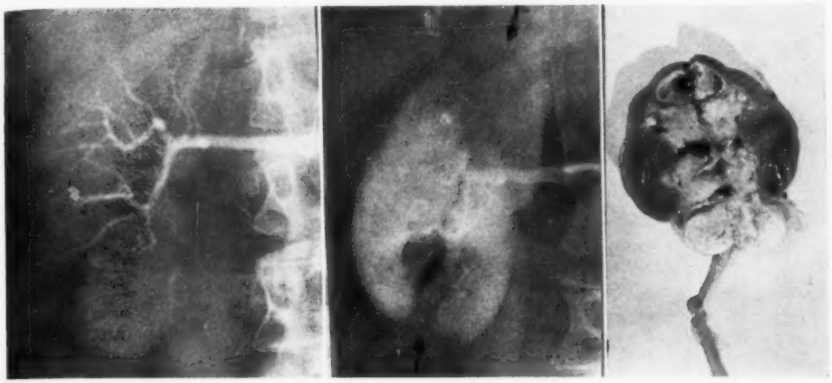

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Fig. 6. Selective angiography in renal tuberculosis. Defects in upper and lower pole. a) Arterial phase, devascularized zones. b) Defects corresponding to lesions and contrast filling of undestroyed parenchyma in mid-portion. c) Specimen. Large foci in upper and lower pole corresponding to roentgen findings.

the lesion. In other cases, as shown in Table 1, there was good correspondence between the angiographic findings and the specimens.

Contrast filling of the parenchyma is better achieved in selective angiographies than in aortographies despite the small amount and relatively low percentage of the contrast medium injected. This may have different causes, but the effect is no doubt more marked in selective angiographies because of the technical factor of the better coning made possible by the smaller area examined. Further, it is well known that the so called nephrographic effect varies according to the capillary or venous phase and to the amount and speed of injection.

In judging changes in the parenchyma, shown as translucencies in the nephrogram, there are many pitfalls. Overlying intestinal gas may be disturbing, and it is recognized that the bowel should be thoroughly cleared before any renal investigation is undertaken. The structure of the kidney itself may also give the impression of defects in the parenchyma. Artificial 'defects' may appear, for instance, when there is an accumulation of contrast medium in the cortex, and the pyramids have not yet been filled. To interpret changes like this, a series of films is needed and, as mentioned before, a film changer to cover all phases of the renal circulation is preferable.

When a series of selective angiographies are performed, difficulties caused by accessory or aberrant vessels will soon be encountered. This happened no less than in 5 out of 23 kidneys with renal tuberculosis. If

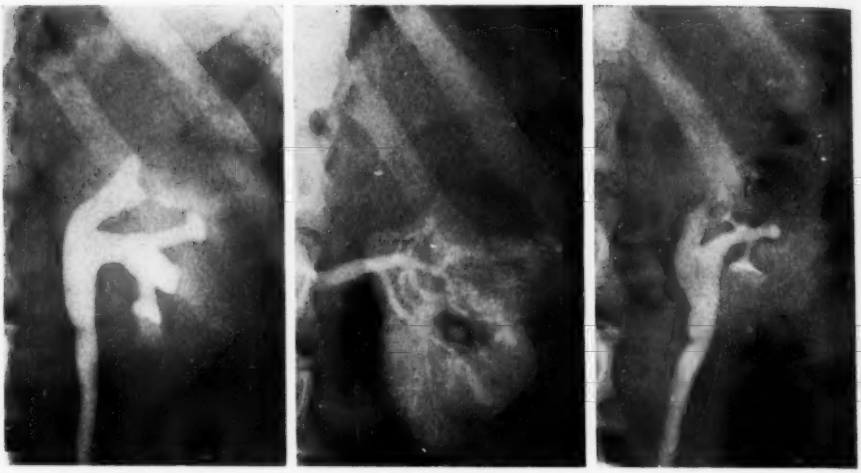

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Fig. 7.

a) Urography. Calyx occlusion and poorly outlined upper pole. (Right kidney was normal.)

b) Selective angiography. Normal detailed pattern in lower two-thirds. Defect and devascularization of upper one-third.

c) After segmental resection. Deformity of renal pelvis, but good function.

d) Huge abscess resected.

the catheter slips into the main artery, the corresponding vessels are filled, and the parenchyma is rendered visible shortly after the injection; at the same time a 'defect' in the parenchyma will appear corresponding to the non-filled area vascularized by the aberrant vessel. This can be easily mistaken for a tuberculous focus if the real cause is not appreciated (Fig. 8). In a case of a tuberculous non-functioning kidney (hydronephrosis) only the aberrant vessel was filled, but the findings confirmed the diagnosis (Fig. 9). Similar findings may also occur where the main artery divides close to the aorta and the catheter slips into one of the branches. Such experiences correspond well to the work of GRAVES in which the segmental

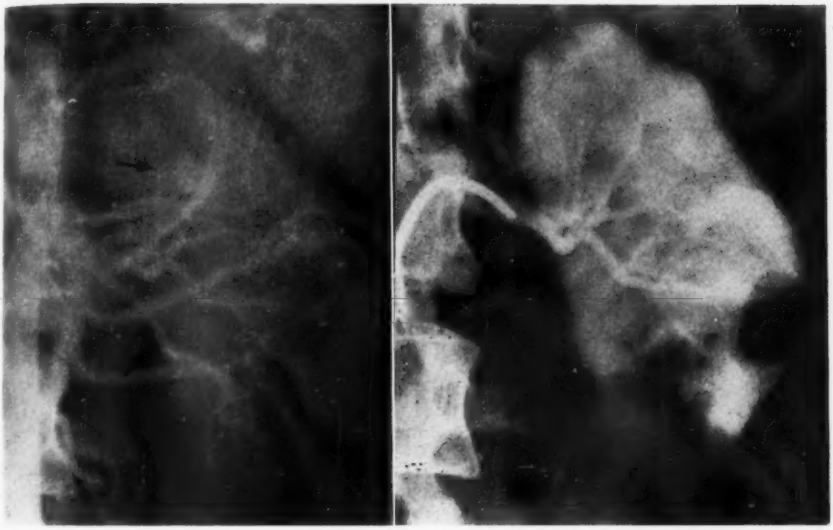

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Fig. 8. a) Aortogram of left kidney. Irregular vessels in upper pole corresponding to small cavity. Aberrant vessel to lower pole. b) Selective angiography. Defect in lower pole due to non-filling of aberrant vessel.

Table 1

Selective angiography in renal tuberculosis; diagnostic reliability of the method (operated cases)

Number of kidneys operated	Total resection	Segment resection	Complete corresp.	Undetected foci	More	Less
17	3	14	12	2	2	2

arrangement of the renal arteries is described, and it is shown that there is no collateral circulation between the segments. The many anatomical variations of the renal vessels should certainly be carefully studied and appreciated to avoid misinterpretation of the findings in selective angiography.

This material is as yet too small to give a complete survey of the diagnostic possibilities, but compared to our earlier experiences, some definite conclusions may now be drawn. Selective angiography takes a

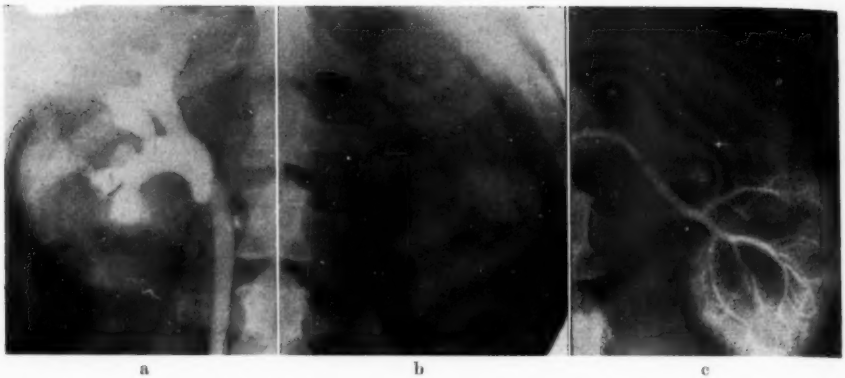

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Fig. 9. a) and b) Tuberculous non-functioning left kidney (hydronephrosis). c) Selective angiography with catheter in lower main artery. The upper branch could not be reached. Typical spread of small vessels as in hydronephrosis. (Confirmed by total resection.)

considerably longer time than the other methods. However, in a well-equipped department and performed by an operator of some experience, the examination should not take more than an hour and sometimes less.

One of the most important questions is whether the method is harmful to the kidney. All cases have been carefully studied as to clinical reactions or late damage. So far we have not observed any complications, untoward reactions, or damage to the kidney. We employ a less concentrated contrast medium than the one usually used for aortography, and only 8 to 10 ml are injected. Furthermore, only one kidney is examined and excretes the contrast medium in selective angiographies, whereas both kidneys are exposed to the action of the medium in aortography. The diagnostic results obtained in the first cases were not entirely satisfactory, but with improvements and greater technical experience, the procedure is now most reliable (Table 2).

Table 2

Value of selective angiography in renal tuberculosis

Number of kidneys examined	Good	Unsatisfactory	Better than aortography	Aberrant vessels	Damage to the kidney
23	20	3	19	5	0

A comparison with conventional aortography cannot readily be made with this material, which is more or less in the nature of a survey. As tabulated here the comparison must therefore be accepted with reservation.

SUMMARY

A short survey is given of the roentgenologic procedures available for the diagnosis of renal tuberculosis. Selective angiography offers a new and, it is suggested, an improved method, especially when segmental resection is planned.

ZUSAMMENFASSUNG

Eine kurze Übersicht über die zur Stellung der Diagnose einer Nierentuberkulose zugänglichen röntgenologischen Untersuchungsmethoden wird gegeben. Die selektive Angiographie bietet eine neue und, wie angenommen wird, verbesserte Methode, insbesondere für die Fälle, in denen eine segmentale Resektion geplant ist.

RÉSUMÉ

L'auteur passe rapidement en revue les techniques radiographiques utilisables pour le diagnostic de la tuberculose rénale. L'angiographie sélective est une méthode nouvelle, et, semble-t-il, meilleure, en particulier quand on envisage de faire une néphrectomie partielle.

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THE DIFFERENTIAL DIAGNOSIS IN THE EXAMINATION OF THE BILIARY DUCTS AFTER CHOLECYSTECTOMY

by

Rolf Köhler

The introduction of intravenous cholegraphy in 1953 marked a great advance in the examination of the biliary passages. A roentgenologic examination of patients who had been subjected to cholecystectomy previously hardly worth attempting, was now rendered possible.

In the cholegraphy of such patients, one diagnostic problem lies in the identification of a possible cystic duct remnant. In the present paper, particular attention will be paid to this structure, which has been dealt with in the clinical literature for a period of over 50 years.

From his observations on an extensive series MILLBOURN (1951) doubted the clinical significance of the remnant. From the literature, however, LARMI & FOCK (1957) collected 241 cases in which a cystic duct remnant was considered the cause of post-cholecystectomy symptoms.

The cystic duct remnant is radiologically demonstrable by cholangiography performed both during and after operation. In exceptional cases it has likewise been demonstrable by means of oral contrast media. Cholegraphy permits of a study of the cystic duct remnant under physiologic conditions, provided that the extrahepatic bile ducts become filled and the passage to the stump is unobstructed.

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GAEBEL & TESCHENDORF (1954), PUHLMANN (1954), SCHÖNBAUER (1954), ORLOFF (SKLAROFF et coll. 1954), STEIN & FINKELSTEIN (1955), GÓMEZ (1955), and FRIED (1956), believed that rounded or oblong accumulations of contrast medium, visible in cholegraphy lateral to the common bile duct, are produced by cystic duct remnants. No other alternative was even considered, although the majority of the cases was not operatively verified.

LUDIN & FEINE (1954) pointed out the possibility of confusion of this structure with the pars superior duodeni. FROMMHOLD (1956) mentioned 'an unusual projection' of the upper flexure of the duodenal loop. FEINE (1955) drew attention to the upper duodenal flexure and the duodenal bulb, while GAEBEL & TESCHENDORF discussed the possibility of filling the bulb with contrast medium, as did HORNYKIEWYTSCH (1956).

These conflicting opinions in the literature concerning the origin of contrast material lateral to the common bile duct in cholegraphy of patients subjected to cholecystectomy seemed to warrant a further attempt at their elucidation. For this purpose the cholegraphies carried out in 1955 and 1956, as well as the postoperative cholangiographies carried out during the same period were surveyed.

There were 104 cholegraphies, 76 of which had been subjected to cholecystectomy. The unoperated cases thus numbered 28; in 16 of these the gallbladder was contrast filled. Thirty postoperative cholangiographies in all were performed.

All cholegraphies were carried out with the patient in the recumbent position with the left side raised about 20° to avoid superimposition of the common bile duct on the spinal column. Forty ml Biligrafin 20 % were generally injected. In postoperative cholangiography, the injection was as a rule given through a T-tube with the patient in the same position and without fluoroscopic control. Roentgenograms were made after the careful injection of 5, 10 and 15 ml of mono-iodized contrast medium 20 % with the patient in slightly varying degrees of rotation.

Cholangiographies seem to be of particular value in this investigation because, in comparison with cholegraphies, the duodenum is better filled with contrast medium and the amount of contrast medium is known. The emptying of the contrast medium into the duodenum is believed to take place fundamentally in the same way in cholegraphy and cholangiography.

Table I

	Number of cases	Cases with accumulation of contrast medium lateral to common bile duct
Cholegraphy		
Gallbladder filled	16	5
Gallbladder not filled	12	3
After cholecystectomy	76	23
Postoperative cholangiography	30	21
Total	134	52

Fig. 1. Cystic duct remnant, about 3 cm long, containing two stones.

It is seen from the table that in about one-third of the cholegraphies and two-thirds of the cholangiographies, contrast medium could be seen outside the extrahepatic bile ducts.

At Surgical Clinic II, from which the clinical material originates, the cystic duct is ligated as close to the common bile duct as is consistent with the avoidance of tension or stretching of the large bile ducts. It is considered justified to leave a cystic stump only if severe inflammatory changes, profuse bleeding, or poor visibility render total extirpation of the cystic duct impossible or dangerous. Consequently, a cystic duct remnant should rarely be found in postoperative cholangiography; only one was observed in the present series. Of the cholecystectomized patients, subjected to cholegraphy, considerably more than a half had been operated on at the clinic. Among the 76 cases, only 2 had cystic duct remnants, both of which were verified by operation. One of these is shown in Fig. 1. One further cystic duct remnant was found at reoperation, but had not been demonstrated roentgenologically owing to poor concentration of the contrast medium.

Thus, out of the 134 cases in the present series only 4 had a cystic duct remnant, while in 52 cases contrast medium accumulations outside the large bile ducts were seen.

Two simple facts must be borne in mind when discussing this phenomenon: 1) When Oddi's sphincter is open, the contrast medium flows into the duodenum; 2) The patient is rotated 20 to 30 degrees to the right to avoid superimposition of the common bile duct upon the spinal column.

The contrast medium flowing into the duodenum passes not only in an aboral direction, but upwards as well. In the series under review the medium spread into the duodenum in both directions in all cases, reaching the upper part of the duodenum in about one-third of the cholegraphies and about two-thirds of the cholangiographies.

The duodenal bulb and the common bile duct are separated by rotating the subject. When the rotation is slight they are still partly superimposed but when the rotation is increased they are separated, the duodenal bulb appearing lateral to the common bile duct (Fig. 2). The bulb will therefore

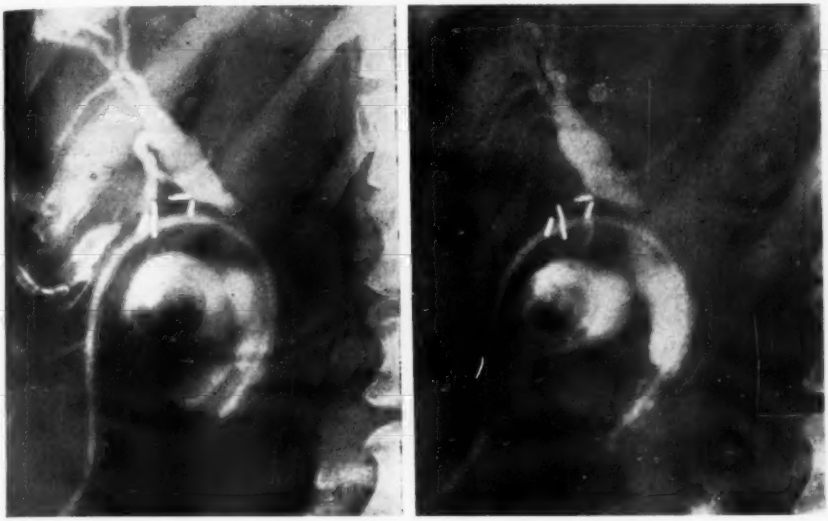

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Fig. 2. a) Postoperative cholangiography. Patient rotated about 15° to the right. Larger bile ducts, duodenal bulb and prepyloric portion of stomach filled with contrast medium. Duodenal bulb and common bile duct partly superimposed. b) About 25° rotation to the right. Duodenal bulb and common bile duct now separated. Blood vessels ligated with silver clips.

appear at about the same site as a cystic duct remnant after cholecystectomy. This is the essential circumstance which should be considered when contrast medium accumulations outside the course of the large bile ducts are to be interpreted in postoperative cholangiographies.

Filling of duodenal diverticula, however, must also be considered, particularly if a diverticulum is situated at the duodenal convexity. They are, however, comparatively rare, and still more uncommon are diverticula of the common bile duct (SJÖGREN 1941, LICHTMAN 1953, LÖRINC & STREHLINGER 1957). An extremely rare finding is a filling of the remaining portion of an incompletely extirpated double gallbladder (MILLBOURN 1941).

A slightly dilated cystic duct remnant no larger than a fingertip, which according to the literature (BERNHARD 1943, LARMI & FOCK 1957) is demonstrated in more than a half of operatively verified cases, has characteristic appearances. The radiologist who is accustomed to look for such formations after cholecystectomies will generally arrive at the diagnosis without difficulty. There will however be considerable diagnostic difficulties when the cystic stump is dilated and perhaps contains

Fig. 3. Cholegraphy. Filling of a large gallbladder, the common bile duct, and the first part of the duodenum.

tissue from the neck or infundibulum of the gallbladder. The stump may be oval or rounded in shape and of considerable size (BERNHARD) and may easily be confused with the first part of the duodenum, particularly since the connection with the common bile duct is often indistinct.

As mentioned above, in about one-third of cholegraphies and two-thirds of cholangiographies contrast medium emanating from the biliary tract could be observed lateral to the common bile duct in the region of the upper part of the duodenum. It formed a rounded, sharply defined accumulation which, I felt, lay in the duodenal bulb. This opinion was based upon three factors: 1) The origin of the contrast medium; 2) Its site and shape; 3) Ten patients in whom the first part of the duodenum seemed to contain contrast medium from the biliary tract were further investigated by means of barium by mouth, and the site of the accumulation verified. In this connection it should be stated that the duodenal bulb may sometimes be recognised without the aid of a barium meal. Furthermore, the appearances of the mucosal folds will often be seen to change from film to film. A gas bubble may occasionally simulate a stone and cause an erroneous diagnosis to be made.

Conclusions

Cholegraphy has increased the interest in and the possibilities of the roentgenologic examination of patients who have undergone cholecystectomy. This comparatively new method of examination has naturally raised certain diagnostic problems, of which the frequency of the filling of a cystic duct remnant and the filling of the duodenal bulb has been a matter of discussion.

In about one-third of the cases examined, a rounded well-defined accumulation of contrast medium appeared laterally near the common bile duct and was shown to lie in the first part of the duodenum. Cystic duct remnants have another appearance. Only large dilated remnants may simulate a contrast-filled duodenal bulb. The occurrence of a cystic duct remnant is dependent on the operative method. If there is any doubt as to the diagnosis, a barium meal examination should be carried out.

SUMMARY

The causes of contrast accumulations outside the large bile ducts, seen in the roentgenologic examination of the biliary tract of patients who have been subjected to cholecystectomy, have been analyzed in series of 134 cholegraphies and postoperative cholangiographies. The differential diagnosis is discussed, and the value of the barium meal examination is pointed out.

ZUSAMMENFASSUNG

Die Ursache der Kontrastanhäufungen ausserhalb der grossen Gallengänge, die man bei der Röntgenuntersuchung der Gallenwege von cholecystektomierten Patienten findet, sind in einer Serie von 134 Cholegraphien und postoperativen Cholangiographien analysiert worden. Die Differentialdiagnostik wird besprochen und der Wert der Bariumbreiuntersuchung wird hervorgehoben.

RÉSUMÉ

L'auteur a analysé sur une série de 134 cholégraphies et cholangiographies postopératoires les causes de l'accumulation de contraste en dehors des grands canaux biliaires que l'on voit au cours de l'examen radiologique des voies biliaires des malades cholécystectomisés. Il étudie le diagnostic différentiel et souligne l'intérêt de l'examen par repas baryté.

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STUDIES ON THE PROTECTIVE ACTION OF CYSTEAMINE AND RELATED COMPOUNDS AGAINST NITROGEN MUSTARD (HN2) INJECTED INTO MICE

by

Aage Juhl Therkelsen

During recent years, comprehensive investigations to find chemical compounds with a protective action against ionizing radiation have been performed. One of the most efficient compounds so far detected is cysteamine (beta-mercaptoethylamine or Becaptan), which was studied by BACQ and his co-workers (2). SALERNO and FRIEDELL (15) have shown that cysteamine also exerts a protective action against nitrogen mustard injected into rats. The mechanisms of the radioprotective effect of cysteamine and its protective action against nitrogen mustard have not been conclusively clarified. From their studies, SALERNO and FRIEDELL drew the following conclusion: 'It appears that the protective action against nitrogen mustard is a result of the direct interaction of the free sulfhydryl groups of cysteine or Becaptan with the cyclic ethylene imonium ion of HN2, but that protection against the biological effects of roentgen rays is mediated indirectly through a reduction of intracellular oxygen tension.' However, DESAIVE and VARETTO-DENOEL (5) claim that both HN2 and cysteamine are bound so rapidly in the organism that a direct reaction between cysteamine and HN2 in the blood or in the extracellular

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fluid is impossible. Studies by ELDJARN and PIHL (7, 8) also suggest that cysteamine is rapidly bound in the organism; these authors express the view that both the radioprotective effect and the protective action of cysteamine against nitrogen mustard may be explained by a temporary linkage of the compound to vital SH groups in the cells, so that these are protected against both the radicals formed by roentgen rays and against nitrogen mustard.

In order, if possible, to throw light on the mechanism of its protective action against nitrogen mustard I have performed a study on the protective effect of cysteamine against HN2 injected into mice. In addition, I have made a 'screening' of the protective effect against HN2 of 10 cysteamine derivatives and two organic amines.

Materials and Methods

The experimental animals were about two-months-old C_3H mice, divided into groups of 10 with an equal number of males and females; their weight ranged from 17 to 23 g and the average weight in the individual groups from 19.3 to 20.2 g. The C_3H mice originate from a pair delivered by the Fibiger Laboratory, Copenhagen, in 1950, and subsequently inbred in Aarhus. The animals were placed separately in glass jars and given water and food ad libitum. The nitrogen mustard used was methyl-bis-beta-chloroethylamine-hydrochloride (HN2) supplied in the form of Erasol by the pharmaceutical laboratory Ferrosan, Copenhagen, in ampoules of 10 mg dissolved in absolute alcohol.

After dilution with physiologic saline, an amount corresponding to LD_{100}, dissolved in 0.1 ml saline, was injected subcutaneously into the nuchal region of the mice with a syringe which automatically delivered that amount with an accuracy of $\pm$ 1 %. The LD_{100} had been determined beforehand as 0.11 mg. In the subsequent experiments this dose was injected, without preceding protection, into 13 groups, each of 10 animals. In two of the groups, one out of 10 animals survived, while all animals in the remaining 11 groups died, *i. e.* the amount injected corresponded to $LD_{98.5}$.

As the experimental animals were inbred and selected as possessing roughly the same weight and age distribution in all the experiments, there may be justification in subjecting all the experiments to a collective statistical analysis. As only two out of 130 mice survived an injection of 0.11 mg HN2, the probability of the survival of 3, 4 or 5 out of 10 animals after this dose can be calculated from the formula

$$\sum_{x=0}^{2} \frac{\binom{130}{x}\binom{10}{5-x}}{\binom{140}{5}}$$

which gave $P = 0.0025$. Three survivors out of a group of 10 animals may therefore be taken as an expression of a statistically significant protection.

The various substances studied for protective action were likewise dissolved in physiologic saline and injected intraperitoneally in an amount of 0.2 ml. The solutions were prepared immediately before use and, if necessary, neutralized with NaOH or HCl. The cysteamine and cysteamine derivatives were synthetized by the Institute of Chemistry of the University of Copenhagen (Prof. K. A. JENSEN). The hydrochlorides of tyramine and tryptamine were supplied by E. MERCK, Darmstadt.

The toxicity of the substances was determined on inbred 'street' mice, because C_3H mice were not available in a sufficient number. Only a rough determination of the toxicity was made, the substances being injected intraperitoneally into groups of six mice, in order to fix the lowest dose capable of killing two to four out of the six animals ($LD_{2-4/6}$). The protection afforded by the various substances was then studied in the C_3H mice, usually by injecting one half of the said toxic dose intraperitoneally 15 minutes before the subcutaneous injection of 0.11 mg HN2. In order to determine the protective action of cysteamine on the bone marrow and spleen, groups of protected and unprotected animals were killed and subjected to autopsy 21 and 96 hours after the injections.

Counts of nucleated cells in the bone marrow were made in sections, 5 μ in thickness, of marrow from the distal end of the femur, fixed in formalin and stained with haematoxylin-eosin. The counts were performed on three sections from each marrow, cut at an interspace of 40 μ; all the cells in three oil-immersion fields (magnification $\times$ 1125) were counted. The total weight of the spleens in each group was determined to the nearest milligram. After fixation of the spleens in formalin and staining with haematoxylin-eosin the ratio of the total area of the cut surface of the spleen to that occupied by the follicles was determined planimetrically after preceding drawing of the outline of the specimens in micro-projection.

Results

A. Protective action of cysteamine against lethal effect of HN2

Diagram 1 shows the number of survivors in five groups of 10 animals into which 3 mg of cysteamine was injected intraperitoneally at various times before and after subcutaneous injection of 0.11 mg HN2.

It is seen that 8 out of 10 mice survived when cysteamine was given a few seconds before and 30 minutes before HN2, whereas injection of cysteamine 60 minutes before the HN2 gave only a slight extension of the survival time, but did not increase the number of survivors.

Injection of cysteamine 10 minutes after HN2 had no effect.

The experimental results were very uniform. In the subsequent experiments the protective effect of cysteamine was checked three times by injection of 3 mg cysteamine 15 minutes before 0.11 mg HN2. In all three experiments, 8 of the 10 mice survived, whereas all the control animals died.

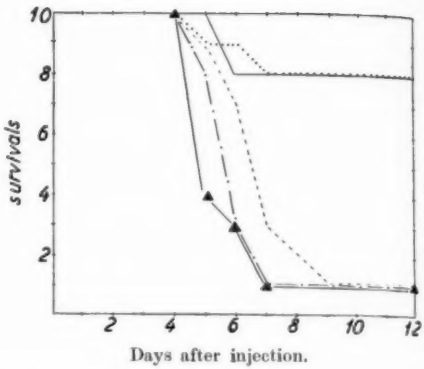
Diagram 2 shows the weight curves for protected and unprotected animals, each curve representing the average weight for one group of 10 animals. It is seen that the weight losses were almost identical in all three groups during the first 3 to 4 days after the injections, and that weight gains in the protected groups did not occur until the first animals in the unprotected group succumbed.

Diagram 3 shows the protective effect of various amounts of cysteamine. All cysteamine injections were given 15 minutes before the administration of HN2. It is seen that 1.5 mg cysteamine afforded only slight protection (3 out of 10 animals survived), and that 0.75 mg cysteamine had no protective effect at all.

Diagram 1.

Survivals in five groups of 10 C_3H mice.
Average weight: 19.8 ± 0.2 g.
3 mg of cysteamine injected:

..... 30 min. before 0.11 mg HN2
——— just » » » »
- - - - - - 60 min » » » »
. — . — . 10 » after » » »
▲——▲ 0.2 ml physiol. saline was injected just before 0.11 mg HN2



B. Protective effect of cysteamine on bone marrow, spleen and intestinal tract

In order to investigate if cysteamine afforded any primary protection of the organs, 5 protected and 5 unprotected animals were killed and examined at 21 and 96 hours on the assumption that the result at 21 hours would reveal differences in the primary destruction, if any, whereas the findings at 96 hours might show a difference in the degree of regeneration, since it was about that time that the weight gains began.

Bone marrow and spleen. The results of two experiments (I and II a) appear from Table 1, in which cell counts in sections of the bone marrow, the average follicle area, and the total weight of the spleens of five animals are shown. In these experiments, 3 mg of cysteamine was injected intraperitoneally 15 min before the subcutaneous injection of 0.11 mg of HN2.

The bone marrow showed a considerable difference in the cell counts in protected and unprotected animals, both at 21 and 96 hours. Thus, cysteamine affords a definite primary protection of the bone marrow.

On the basis of the present material it cannot be decided whether there is any primary protection of the spleen, even though both the weight of the spleens and the follicle areas suggest the presence of a weak primary protection. That there is, on the other hand, a fairly great difference between protected and unprotected spleens at 96 hours is unquestionable and appears distinctly from Fig. 1, which shows a protected and an unprotected spleen at that time. In the unprotected spleens, only remnants of the follicles are present, whereas the protected spleens show many regenerating follicles.

In continuation of the experiment II a 3 mg of cysteamine and 0.11 mg of HN2 were mixed in vitro and then injected intraperitoneally as rapidly as possible (within 3 min) into a group of 10 animals, of which

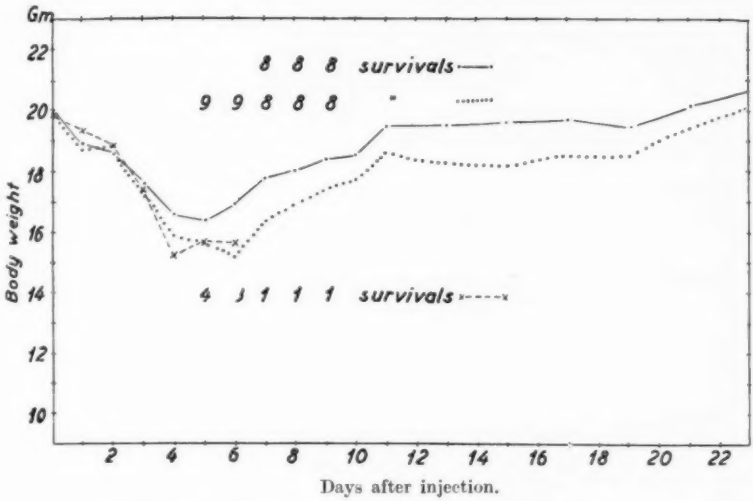


Diagram 2. Average weights in three groups of 10 C_3H mice.

. . . . . 3 mg cysteamine 30 min. before 0.11 mg HN2.
•————• » » just » » » »
x - - - - x physiol. saline just before » » » »

5 were autopsied at 21 hours and the remaining 5 at 96 hours. The bone-marrow cell counts and the spleen weights are recorded in Table 1 as experiment II b. It is seen that both the cell counts and the weights of the spleens are considerably higher here than in experiment II a, in which cysteamine was injected intraperitoneally 15 minutes before subcutaneous HN2 injection.

In another experiment all 10 mice survived when the two substances were mixed in vitro before the injection. In all probability, during the brief time interval (from a few seconds to about 3 min) between the mixture of the two substances and the injection, part of the HN2 is inactivated by being linked up with the SH group of cysteamine.

Small intestine. The intestinal tissue selected for histologic study was in all cases taken from the distal part of the ileum, since, according to GRAEF et coll. (10), the degenerative changes following injection of nitrogen mustard are most pronounced in the ileum. At 21 hours, severe degenerative changes had occurred both in the protected and unprotected animals, especially in the Lieberkühn crypts where the cytoplasm of the epithelial cells is distended by large, clear vacuoles, and numerous pyknotic and fragmented nuclei are present (Fig. 2). The interstitial

Diagram 3.

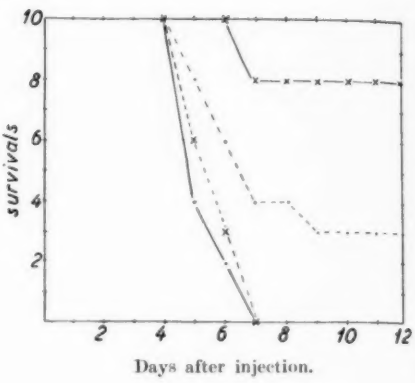
Survivals in four groups of 10 C_3H mice.
Average weight: 19.6±0.1 g.
Cysteamine in different amounts injected 15 min before injection of 0.11 mg HN2:

x ——— x 3 mg

. — — . 1.5 »

x — — x 0.75 »

. ——— . physiol. saline 15 min before 0.11 mg HN2.



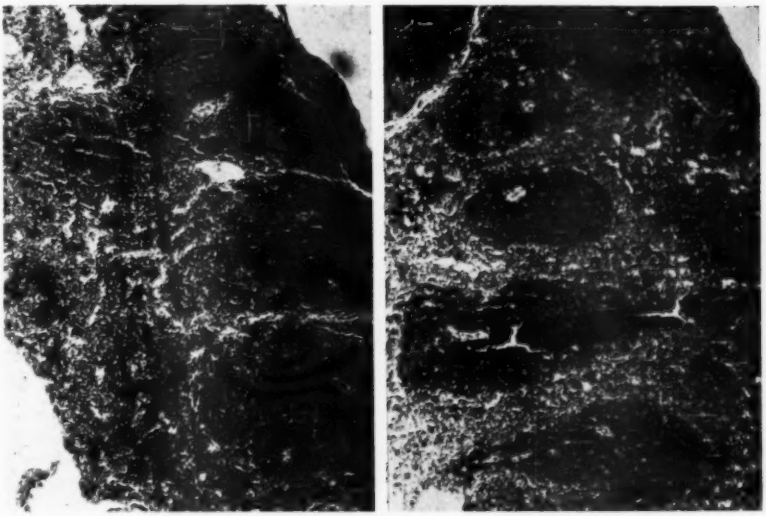
tissue shows marked oedema, but no inflammatory reaction. Mitoses are absent.

The villi are short and broad-based, whereas the surface epithelium is apparently well preserved. A comparative microscopic study of intestinal tissue from protected and unprotected animals does not disclose any definite difference in the degree of the degenerative changes, but a small quantitative difference cannot be excluded by this method.

On the other hand, a marked difference between the intestines from protected and unprotected animals is visible at 96 hours.

The intestinal tissue from unprotected animals shows severe changes (Fig. 3). The villi have almost disappeared, and their remnants are seen as low, broad-based projections on the surface of the mucosa. The surface epithelium is flattened and the site of severe degenerative changes. The cytoplasm contains many vacuoles, and the nuclei show all sorts of degenerative changes ranging from lobulation to pyknosis and fragmentation. In most places, the Lieberkühn crypts have completely disappeared and have often been replaced by large cysts in the lamina propria surrounded by flattened fibroblasts. The lamina propria is increased in width, with a relatively small number of cells. The cells are almost exclusively fibroblasts of normal appearance, surrounded by wide bands of connective-tissue fibrils. Lymphocytes and polynuclear leukocytes are either compeletely absent or present only in very small numbers.

In the protected animals the picture is quite different (Fig. 4). The villi here too have, however, almost disappeared, and the surface epithelium shows degenerative changes similar to those observed in the unprotected animals. On the other hand, the crypts are largely preserved, and numerous mitoses are seen in their epithelium. The cellular content



a b

Fig. 1. a) Section from an unprotected spleen 96 hrs after injections: only remnants of the follicles. b) Section from a protected spleen 96 hrs after injections: many regenerating follicles. (Haematoxylin-eosin. About × 44.)

of the lamina propria is considerably higher than in the intestines of unprotected animals; in addition to fibroblasts, many plasma cells, lymphocytes and polynuclears are present.

C. Protective effect of various cysteamine derivatives

The protective action of various cysteamine derivatives against nitrogen mustard was studied by the same technique as had been used for cysteamine in the hope that this might throw some light on the mechanism of the protective action. The results appear from Table 2.

It is seen (experiment 1) that *methyl-bis-beta-mercaptoethylamine*, which can be derived from HN2 by replacing its two chlorine atoms with SH groups, does not afford any protection, but that it is so toxic that it can only be given in amounts which are about a seventh of the cysteamine dose used.

S-methyl-cysteamine is about three times less toxic than cysteamine, but has in the dosage used (three times as high as that of cysteamine) no protective effect. On the contrary, the substance seems to shorten the survival time of the animals (on an average, by 1.7 days).

Table 1

The total weight of 5 spleens, the ratio of the total area of the cut surface of the spleens to that occupied by the follicles (average of 5 spleens) and counts of nucleated cells in sections of the bone marrow (average of 5 animals; the count for each animal being average of 3 sections) 21 and 96 hours after the injections in protected and unprotected C_3H mice.

	Experiment No.	Autopsy: 21 hours		Autopsy: 96 hours		Normal controls
		Protected	Unprotected	Protected	Unprotected	
Weight of 5 spleens (mg) ...	I	143	136	129	73	316
	II a	149	141	158	106	—
	II b	222[1]	—	193[1]	—	—
Area of intact surface/area of lymphoid follicles	I	3.81 (3.46—4.07)	4.20 (2.81—5.16)	—	—	3.51 (2.97—4.32)
Cell number in sections of bone marrow (three oil-immersion fields)	I	653 (543—764)	376 (273—464)	242 (209—213)	125 (118—141)	Too many cells for counting
	II a	624 (516—797)	441 (407—499)	190 (135—265)	136 (116—162)	
	II b	756[1] (675—879)	—	544[1] (352—640)	—	

[1] Cysteamine and HN2 mixed in vitro.

N-dimethyl-cysteamine (experiments I and II) has a protective effect which in equimolar amounts is considerably greater than that of cysteamine, since 2×10^{-2} mM of the substance gives a better protection than 3.9×10^{-2} mM of the cysteamine base. The toxicity of the substance is about twice as high as that of the cysteamine base.

N-propyl-cysteamine and *N-isopropyl-cysteamine* (experiment III) are nearly twice as toxic as N-dimethyl-cysteamine and have a protective effect of almost the same order or, perhaps, a little greater (Cf. experiments IV and V, in which N-dimethyl-cysteamine and N-isopropyl-cysteamine were given in equimolar amounts).

N-butyl-alpha-methyl-cysteamine (experiment VI) is about five times as toxic as cysteamine and seems to have a somewhat greater protective effect, since 3 out of 10 animals survived ($P < 0.0025$) after an amount of 0.82×10^{-3} mM, while cysteamine did not show any protective effect in an amount of 0.75 mg, which corresponds to 1.0×10^{-2} mM (Fig. 3).

N-hexyl-alpha-methyl-cysteamine (experiment VI) is about nine times as toxic as cysteamine, but it did not show any definite protective effect in the dosage used.

Table 2

Results of some experiments on the protective effect of various cysteamine derivatives, tryptamine and tyramine against the lethal effect of HN2 in C_3H mice. The 'protective' compounds were injected intraperitoneally 15 min before the subcutaneous injection of a $LD_{98.5}$ of HN2. The number of surviving mice out of 10 and the $LD_{2-4/6}$ in 'street' mice are stated. Average survival time in days is given for the controls and for groups where no protection was obtained.

Experiment No.	Compound	Dose		$LD_{2-4/6}$ in 'street' mice mg	Survivals out of 10 mice after 30 days	Average survival time in days
		mg/mouse	mM/mouse			
I	Cysteamine [1]	3.0	3.9×10^{-2}	6.5	8	—
	Methyl-bis-beta-mercaptoethyl-amine	1.0	5.3×10^{-3}	2.0	0	6.1
	N-dimethyl-cysteamine	3.0	2.1×10^{-2}	6.0	10	—
	S-methyl-cysteamine	15.0	1.2×10^{-1}	30.0	0	4.2
	Controls	—	—	—	0	5.9
II	N-dimethyl-cysteamine	3.0	2.1×10^{-2}	6.0	10	—
	» » »	2.0	1.05×10^{-2}	—	5	—
	» » »	1.0	0.7×10^{-2}	—	0	5.6
	Controls	—	—	—	0	5.6
III	N-propyl-cysteamine	1.75	1.1×10^{-2}	3.5	5	—
	N-isopropyl-cysteamine	2.0	1.3×10^{-2}	4.0	6	—
	N-beta-mercaptoethyl-piperidine	0.625	3.5×10^{-3}	1.25	2	—
	Controls	—	—	—	1	4.4
IV	N-beta-mercaptoethyl-piperidine	0.625	3.5×10^{-3}	1.25	0	6.1
	N-isopropyl-cysteamine	2.0	1.3×10^{-2}	4.0	6	—
	N-dimethyl-cysteamine	1.82	»	6.0	5	—
	Controls	—	—	—	0	5.8
V	N-benzyl-cysteamine	2.0	1.0×10^{-2}	4.0	0	5.2
	N-beta-mercaptoethyl-morpholine	4.0	2.2×10^{-2}	8.0	0	3.8
	N-isopropyl-cysteamine	2.0	1.3×10^{-2}	4.0	5	—
	N-dimethyl-cysteamine	1.82	»	6.0	3	—
	Controls	—	—	—	0	4.7
VI	N-butyl-alpha-methyl-cysteamine	1.5	8.2×10^{-3}	3.0	3	—
	N-hexyl-alpha-methyl-cysteamine	1.0	4.7×10^{-3}	2.0	1	—
	Controls	—	—	—	0	5.7
VII	Tyramine	1.73	1.0×10^{-2}	—	0	5.1
	Tryptamine	1.96	»	—	0	4.2
	Controls	—	—	—	0	5.6

[1] The cysteamine base was used, whereas all the other compounds were hydrochlorides.

Fig. 2. Section from small intestine of an unprotected animal 21 hrs after injections. Severe degenerative changes, especially of the Lieberkühn crypts: the cytoplasm is distended by large, clear vacuoles, and numerous pyknotic and fragmented nuclei are present. (Haematoxylin-eosin × 300.)

N-beta-mercaptoethyl-piperidine (experiment III) is even more toxic (about 12 times as toxic as cysteamine and about three times as toxic as N-propyl-cysteamine). The substance has no definite protective action in the low dosage in which it can be used. The first experiment (III) pointed in the direction of a weak protective effect, while no effect at all was demonstrated in a subsequent experiment (IV). Neither cysteamine nor N-dimethyl-cysteamine showed any protective action in the corresponding dosage (Cf. Fig. 3 and Table 2, experiment II).

N-beta-mercaptoethyl-morpholine (experiment V) did not show any protective effect. This substance should be compared with N-beta-mercaptoethyl-piperidine, from which its formula can be derived by replacing a CH_2 group with an oxygen atom. This modification seems to cause a considerable reduction in the toxicity (to about one sixth), but

no protective effect is obtained — on the contrary, the substance seems to shorten the survival time of the animals.

N-benzyl-cysteamine (experiment V) shows a toxicity of the same order as N-propyl-cysteamine, but has no protective effect.

Finally, it is seen (experiment VII) that *tyramine* and *tryptamine* do not afford any protection against HN2. As shown by ALEXANDER et coll. (1), these two drugs give good protection against roentgen rays in the dosage used.

Discussion

The protective action of cysteamine against the effect of nitrogen mustard in mice may be explained in different ways. NELSON (13) claimed that cysteamine produces a shocklike condition in the mice. As stated by SCOTT (16), it might then be conceived that due to the mild shock with diminished peripheral blood flow the absorption of the nitrogen mustard is slowed down. A greater part of the nitrogen mustard will therefore be able to react with the subcutaneous tissue, so that a smaller amount will be absorbed. This explanation seems unlikely considering that SALERNO and FRIEDELL (15), in experiments with rats into which the nitrogen mustard was injected intravenously, obtained a cysteamine protection of the same order as that observed in the present experiments. On the basis of this theory it would also be very difficult to explain the results for the various cysteamine derivatives in Table 2.

From their experiments, SALERNO and FRIEDELL concluded that the effect probably consists in a simple inactivation of the nitrogen mustard by its linkage to the free SH group of cysteamine. It would be expected that such an inactivation would occur in vitro, and the results in Table 1 (experiment II b) also suggest that it occurs fairly rapidly.

It is more uncertain if such a simple inactivation is possible in vivo. It is claimed, *e. g.* by DESAIVE and VARETTO-DENOEL (5), that both cysteamine and HN2 are bound to the tissue cells so rapidly that an interaction between the two substances in the blood or in the extracellular fluid is impossible.

Investigations by ELDJARN and PIHL (7) point in the same direction; these investigators showed that 15 minutes after intraperitoneal injection of a protective dose of cysteamine into mice more than 60 per cent of the cysteamine in the blood was bound to the serum proteins or to the proteins of the red cells. They also showed that only negligible amounts are excreted in the urine during the first hour after the injection of the substance into human beings (7, 8), which suggests that the greater part of the substance is rapidly bound in the organism and is therefore not filterable. ELDJARN and PIHL (7) claim that the most plausible explana-

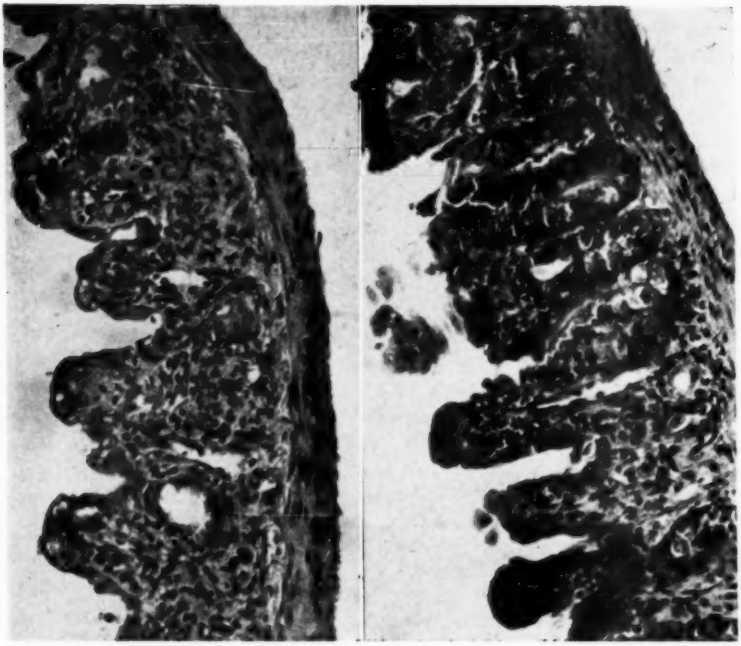


Fig. 3 Fig. 4

Fig. 3. Section from small intestine of unprotected animal 96 hrs after injections. The villi have almost disappeared; their remnants are seen as low, broad-based projections on surface of the mucosa. Surface epithelium shows severe degenerative changes. Lieberkühn crypts replaced by cysts in lamina propria, surrounded by flattened fibroblasts. The lamina propria is thickened and poor in cells, almost exclusively fibroblasts of normal appearance surrounded by wide bands of connective tissue fibrils. (Haematoxylin-eosin. × 150.)

Fig. 4. Section of small intestine of a protected animal 96 hrs after injections. Only scattered short, plump villi are seen, and the surface epithelium is the site of severe degenerative changes, whereas the Lieberkühn crypts are relatively well preserved. (Haematoxylin-eosin. × 150.)

tion of the protective action of cysteamine against both ionizing radiation and nitrogen mustard is that the substance forms mixed disulphides by linkage to SH groups on the cell proteins, by which these are protected against the radicals formed by the roentgen rays and against the action of nitrogen mustard. However, it has not been proved that the mechanisms by which cysteamine protects against the radiation and against nitrogen mustard are identical.

In this connexion it is reasonable to emphasize certain points of resemblance between the present experiments and corresponding investigations on the radioprotective effect of cysteamine and cysteamine derivatives performed by others.

The protective effect of cysteamine against nitrogen mustard and roentgen rays are roughly of the same order of magnitude. ALEXANDER, BACQ et coll. (1) found that 97 out of 100 mice survived a LD_{100} of roentgen rays when they had been injected with cysteamine in a dose of 150 mg/kg before the irradiation. In the present experiments, 32 out of 40 mice, *i. e.* 80 per cent, survived after a LD_{100} of nitrogen mustard.

As shown in Diagram 2, the initial weight loss after a LD_{100} of HN2 is of the same size in protected and unprotected animals, exactly as in the corresponding experiments with roentgen rays (3, p. 316).

In the study of the radioprotective effect of various sulphydryl compounds it has also been difficult to demonstrate any definite difference in the primary destruction of the organs in protected and unprotected animals (3, p. 318), which made CRONKITE (4) advance the hypothesis for glutathione that this substance did not diminish the primary destruction of the organs, but protected factors which were of importance in the regeneration. However, GEREBTZOFF and BACQ (9) believed they were able to demonstrate a primary protection of the liver and spleen afforded by cysteamine, but found no primary protection of the thymus and intestine. The presence of a slight difference in the primary destruction obviously cannot be excluded; such a difference might perhaps be disclosed if it were possible to develop accurate quantitative histological methods.

As shown in Table 1, it can scarcely be doubted that cysteamine reduces the primary destruction of the bone marrow caused by the nitrogen mustard.

I have been unable to trace reports in the literature dealing with the problem whether or not cysteamine similarly reduces the primary destruction of the bone marrow caused by roentgen rays. On the other hand, DEVIK (6) has shown that cysteine reduces the number of chromosomal abnormalities in the bone-marrow cells when it is administered before the irradiation; furthermore detailed studies by PATT et coll. (14) suggest that cysteine given before the roentgen irradiation reduces the primary destruction of the bone marrow caused by the latter in mice, as judged from cell counts in the peripheral blood.

The results of the present study on the protective action of cysteamine derivatives against nitrogen mustard also show points of resemblance to those obtained in the study of the radioprotective action of a number of cysteamine derivatives by LANGENDORFF, KOCH and HAGEN (11), (12).

From their investigations, these authors concluded (11, p. 246) that 'the sulphydryl group is activated by the neighbouring amino group to an increasing extent as the latter is made more strongly positive by substitution; this is indicated by increased toxicity and protective ability. The amino group can be weakened by acid-peptide linkages and by phenyl substitution. The protective ability is then lessened.' They found that the

toxicity increased from monomethyl- through dimethyl- and diethyl- to dipropyl-cysteamine. The radioprotective efficiency increased parallel with the toxicity 'until finally the toxicity of dipropyl-cysteamine is too great to allow the administration of a protective dose'. Thus, the observation that the radioprotection increases with the positivity of the amino group applies, at any rate, only up to a certain point.

From my preliminary studies on the protective action of cysteamine derivatives against nitrogen mustard it can only be concluded that the protective action against nitrogen mustard can be augmented by increasing the positivity of the amino group, since dimethyl-, propyl-, isopropyl- and N-butyl-alpha-methyl-cysteamine had a stronger protective effect than cysteamine given in equimolar amounts.

It also appeared that N-substitution by a benzyl radical abolished the protection against nitrogen mustard; likewise, KOCH and HAGEN (11, p. 246) found that N-phenyl-cysteamine had no radioprotective effect.

As shown in Table 2 (experiment I), S-methyl-cysteamine had no protective action against nitrogen mustard, but rather seemed to sensitize the animals to nitrogen mustard, as judged from the survival times. This observation requires closer investigation, but it should be mentioned that LANGENDORFF, KOCH and HAGEN (12) obtained results suggesting that N,S-diacetyl-cysteamine exerted a weak sensitizing effect to roentgen rays as judged from the number of surviving mice.

With regard to the toxicity of the cysteamine derivatives as assessed by their lethal effect on 'street' mice, Table 2 shows that the toxicity of the substances increases with the positivity of the amino group, while the introduction of an electronegative group (N-beta-mercaptoethyl-morpholine) results in a reduction in the toxicity.

The two derivatives with the highest toxicity (N-hexyl-alpha-methyl-cysteamine and N-beta-mercaptoethyl-piperidine) had no protective action against nitrogen mustard.

It is unknown why the toxicity of the cysteamine derivatives increases with the positivity of the amino group. The lipoid solubility of chemical compounds is usually increased by the attachment of methyl or phenyl groups, while it is decreased by the introduction into the molecule of an electronegative group. As the lipoid solubility of chemical compounds influences, *inter alia*, their ability to penetrate cell membranes, a parallelism between the toxicity and lipoid solubility is not unlikely, but the cause of the lethal effect of the cysteamine derivatives is unknown and, in particular, it is not known whether it is a systemic effect or an effect at cellular level.

While the present preliminary investigations suggest that good agreement exists between the radioprotective effect of cysteamine and cysteamine derivatives and their protective action against nitrogen

mustard, it was not possible, as appears from Table 2, to demonstrate a protective effect against nitrogen mustard of tyramine and tryptamine in doses which afford good protection against roentgen rays (1).

As claimed by VAN BEKKUM and DE GROOT (18), the radioprotective action of the organic amines is possibly due to a systemic effect, since, for example, beta-phenyl-ethylamine is radioprotective in animal experiments, but has no protective effect on isolated cells.

Thus, even though good agreement has been demonstrated between the radioprotective effect of cysteamine and cysteamine derivatives and their protective action against nitrogen mustard, the present investigation obviously does not exclude that protection against roentgen rays and nitrogen mustard is mediated by two different mechanisms, as claimed by SALERNO and FRIEDELL (15). If the explanation of the protective action of cysteine and cysteamine against nitrogen mustard should be a simple inactivation of the nitrogen mustard, it might be expected that injection of the two substances shortly before the administration of nitrogen mustard would reduce the tumour-inhibiting effect of the latter. However, WEISBERGER et coll. (18) claim that administration of cysteine shortly before HN2 in patients with various malignant disorders does not result in any reduction of the tumour-inhibiting effect of HN2. In our laboratories, experimental investigations are in progress aiming at elucidating the influence of cysteamine on the antineoplastic effect of nitrogen mustard in transplanted mouse tumours.

Conclusions

The protective action of cysteamine against the nitrogen mustard methyl-bis-beta-chloroethylamine-hydrochloride (HN2) has been studied in C_3H mice. In four experiments, eight out of 10 mice survived after the administration of a dose of HN2 corresponding to $LD_{98.5}$ when cysteamine in an amount of 150 mg/kg was injected from 0 to 30 minutes before the HN2. Injection of cysteamine 10 minutes after HN2 had no protective effect. The injection of cysteamine resulted in a reduction in the primary destruction of the bone marrow (at 21 hours), whereas it was not possible to demonstrate any definite reduction in the primary destruction of the small intestine and the spleen.

The protective action against HN2 of N-dimethyl-, N-propyl- and N-isopropyl-cysteamine is about twice as great as that of cysteamine; N-butyl-alpha-methyl-cysteamine had some protective effect when administered in a dose in which cysteamine had no effect.

N-benzyl-cysteamine and S-methyl-cysteamine had no protective effect. The toxicity of cysteamine derivatives, as judged by their lethal effect on 'street' mice, seems to increase with the number of carbon atoms attached to the amino group. It is suggested hypothetically that the

toxicity of the substances depends on their lipoid solubility and thus, perhaps, on their ability to penetrate cell membranes. Certain points of resemblance between the results of the present investigation and similar studies on the radioprotective effect of cysteamine and cysteamine derivatives performed by others are emphasized. The investigations reported here did not disclose any evidence suggesting that the protection afforded by cysteamine against HN2 and roentgen rays is due to different mechanisms, as claimed by SALERNO and FRIEDELL (15), but the results obtained do not exclude the possibility that such a difference exists.

Tyramine and tryptamine were studied in one experiment, but these substances did not reveal any protective action against nitrogen mustard.

Acknowledgment

This investigation was carried out under a Lady Tata Memorial Scholarship. It was also supported by a grant from the Research Council of the Danish Civil Defence Board, which is gratefully acknowledged. I am greatly indebted to Anne Gelting, cand. act., for her assistance in the statistical analysis of the material.

SUMMARY

Investigations into the protective action of cysteamine against nitrogen mustard (HN2) are described. A selective protection upon the bone marrow as compared with the small intestine and spleen was observed. The comparative protective action of related agents is discussed in detail and an explanation is put forward for the variation in the toxicity of these substances, as judged by their effect upon mice.

ZUSAMMENFASSUNG

Untersuchungen über die Schutzwirkung des Cysteamines gegen Stickstoff-Lost (HN2) werden beschrieben. Ein selektiver Schutz für das Knochenmark, im Vergleich mit dem Dünndarm und der Milz, wurde beobachtet. Die komparative Schutzwirkung ähnlicher Stoffe wird eingehend diskutiert, und eine Erklärung für die Variation der Giftigkeit dieser Substanzen, beurteilt durch ihre Einwirkung auf Mäuse, wird vorgelegt.

RÉSUMÉ

L'auteur décrit ses recherches sur l'effet protecteur de la cystéamine contre la moutarde à l'azote (HN2). Il a observé une protection élective de la moëlle osseuse par rapport à l'intestin grêle et à la rate. Il étudie en détail l'action protectrice comparée des agents apparentés et propose une explication des différences de toxicité de ces substances que montre leur effet sur la souris.

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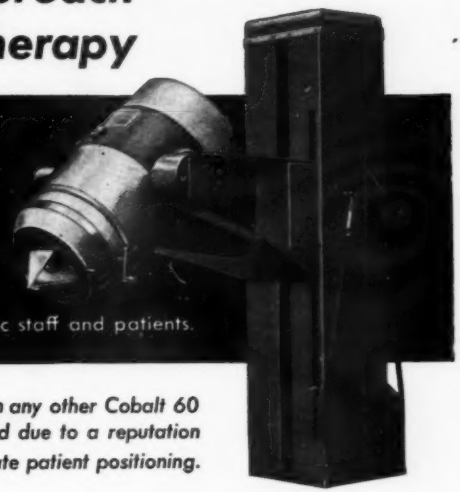

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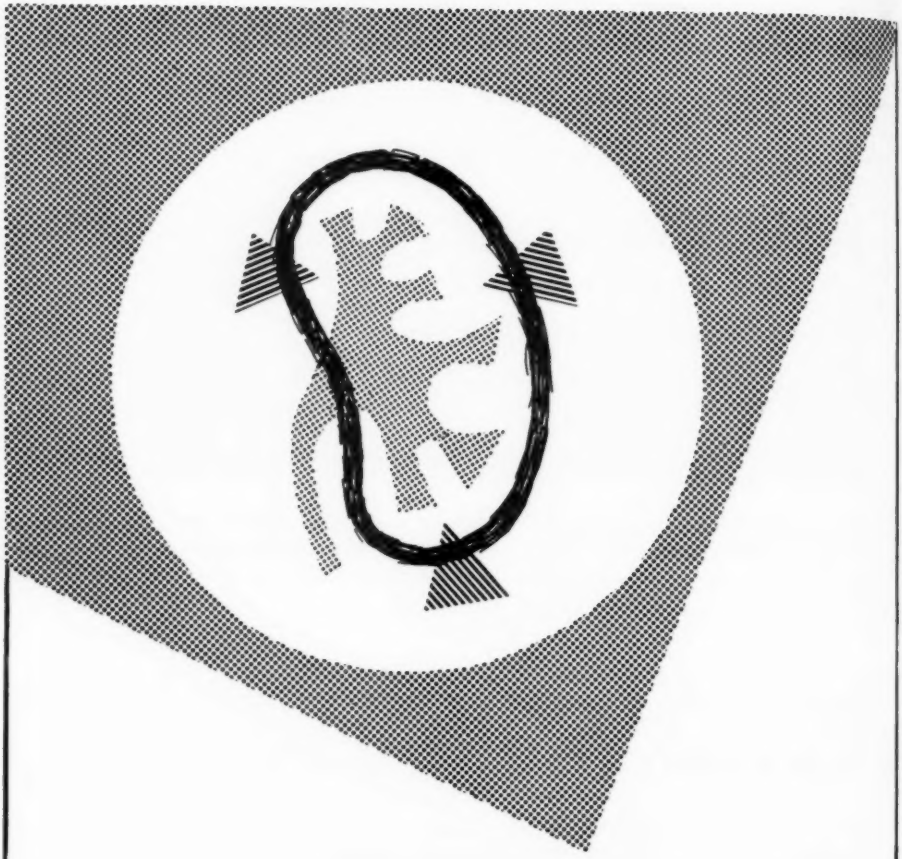

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FROM RADIUMHEMMET (DIRECTOR: PROF. SVEN HULTBERG) AND THE MEDICAL CLINIC (DIRECTOR: PROF. NANNA SVARTZ), KAROLINSKA SJUKHUSET, STOCKHOLM

IN VIVO LOCALIZATION OF COLLOIDAL Au^{198} INTRAVENOUSLY INJECTED IN POLYCYTHEMIA VERA

A preliminary report

by

Lars Engstedt, Sixten Franzén, Lars Jonsson and *Lars-Gunnar Larsson*

The distribution in the body of intravenously administered colloids, which is thought to depend largely upon reticulo-endothelial activity, has been studied only to a very limited extent in living human subjects. Colloidal thorium has long ago been shown to concentrate in the liver and spleen (9). During recent years many studies have been published on the elimination from the blood of intravenously injected colloidal Au^{198}, but these studies relate almost exclusively to the liver. If a small amount of colloid of suitable particle size is used, most of it is rapidly taken up by the liver, and the elimination rate can be used for calculation of the liver blood flow. (For a recent study see KROOK 1956.) The uptake of colloidal Au^{198} in the liver has also been utilized for scintillographic in vivo studies of this organ (1).

Post-mortem investigations on the distribution of colloidal $Mn^{52}O_2$ (in 13 patients) and of colloidal Au^{198} (in 2 patients) have been described (2, 10). In most cases about 90 per cent of the substance was removed

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by the liver, and about 5 per cent each by the spleen and by the remainder of the reticuloendothelial system.

The fate in the body of intravenously injected radioiron bound to plasmaproteins is also considered to depend at least partly upon the activity of the reticulo-endothelial system, and has been studied with external measurements over various organs, including certain bone marrow sites (3, 4).

We have studied the distribution of intravenously administered colloidal Au^{198} in a number of patients with a scintillograph, which permits convenient registration over the whole body (5, 7). This is a preliminary report on the findings in polycythemia vera.

Technique. Colloidal Au^{198} from Amersham was used. According to the supplier the average particle size was about 20 to 25 mμ and the specific activity of the fresh material about 10 mC/mg gold. At the time for the injection the age of the suspension varied up to 8 days (about three half-lives) and the minimum specific activity used was thus about 10 mC/8 mg gold.

The tracer dose was 2 mC, which was regarded as justified in patients planned for internal P^{32} treatment or previously treated in this way. As controls we used patients with locally advanced oral carcinomas, who were in good general condition, and who had no signs of liver or bone involvement. The tracer dose was given intravenously followed after 24 hours by scintillographic examination.

Due to the different order of magnitude of the counting rates over liver, spleen, and bone marrow, a good scintillogram of these three systems could not be obtained simultaneously. The ideal was three scintillograms, in which the working factors of the scintillograph (collimator, scaling factor, speed) were adjusted to the counting rates over liver, spleen and bone marrow respectively. For the sake of simplicity, however, often only two scintillograms were made, one with special regard to liver-spleen and one with special regard to the bone marrow. For the liver-spleen scintillograms a collimator with a diameter of 1.2 cm was used. In order to increase sensitivity a diameter of 2.4 cm was instead used for the bone marrow scintillograms. The wide diameter reduced of course the resolution power which explains the enlargement of liver and spleen in the bone marrow scintillograms. The single-channel pulse height analyzer of the instrument was adjusted to the 411 keV photo peak of Au^{198}. All scintillograms were recorded in the scale 1 : 5.

In the four controls examined the highest counting rates were, as expected, obtained over the liver. The counting rates were also increased over the spleen, pelvis, spine, skull, and thorax (Fig. 1) but to much less extent than over the liver. Nineteen patients with polycythemia vera with a relapse or remission were studied. The uptake of the isotope in the spleen was usually higher than in the controls but, in these patients as well, small compared to the uptake in the liver. As regards the uptake in the bone marrow it was, with the technique used, difficult to compare the central parts of the bone system in the pathologic cases and the controls. The most striking difference between these two groups was, however, the extension of the uptake into the peripheral bones. While in the controls, the uptake usually was concentrated to the central parts

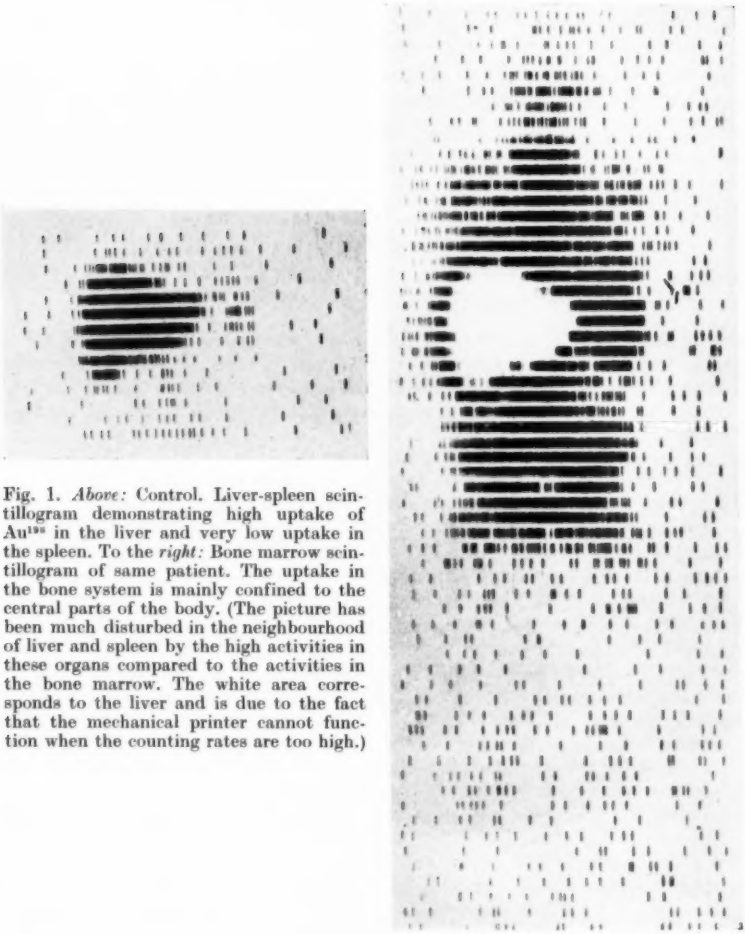

Fig. 1. *Above:* Control. Liver-spleen scintillogram demonstrating high uptake of Au^{198} in the liver and very low uptake in the spleen. To the *right:* Bone marrow scintillogram of same patient. The uptake in the bone system is mainly confined to the central parts of the body. (The picture has been much disturbed in the neighbourhood of liver and spleen by the high activities in these organs compared to the activities in the bone marrow. The white area corresponds to the liver and is due to the fact that the mechanical printer cannot function when the counting rates are too high.)

of the bone system the polycythemia vera patients, both with relapse and remission, showed a great variation and had often a considerable uptake also in the long bones, sometimes especially marked in the epiphyses (Figs. 2 and 3).

Uptake of colloidal Au^{198} in the bone system undoubtedly indicates the presence of active reticulo-endothelial cells, which in these cases means active hematopoiesis. It may thus be possible to localize active bone marrow by help of the intravenous administration of colloidal Au^{198}.

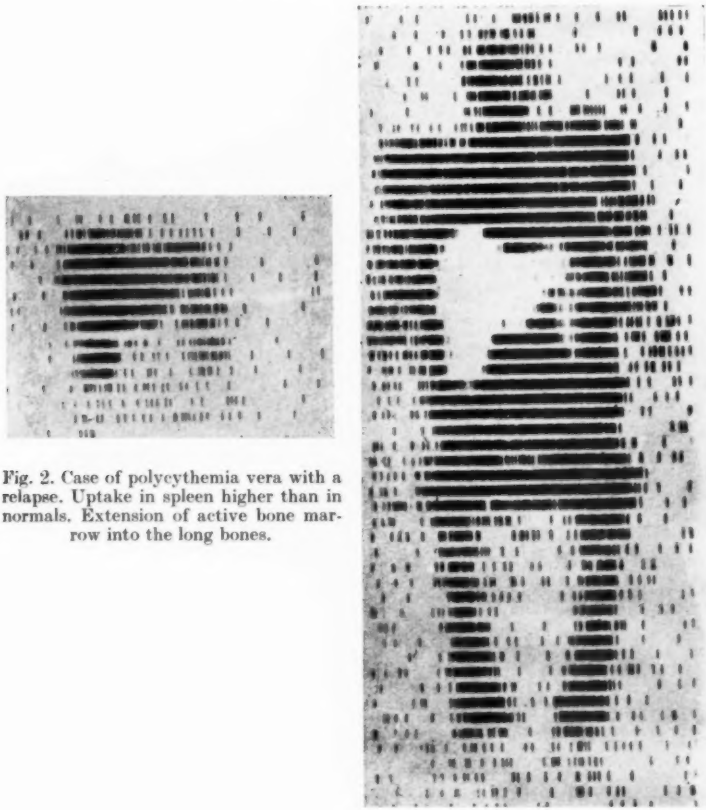

Fig. 2. Case of polycythemia vera with a relapse. Uptake in spleen higher than in normals. Extension of active bone marrow into the long bones.

In polycythemia vera there is often an extension of red marrow to otherwise inactive sites, *e. g.* the long bones, as suggested by external measurements after the administration of Fe^{59} (8). No scintillographic demonstration of the extension of the active bone marrow has, however, previously been reported. Colloidal Au^{198} presents certain advantages over Fe^{59} for this type of investigation. The half life is short (2.7 days as against 46.3 days for Fe^{59}), thus permitting higher tracer doses and more convenient measurements. Colloidal Au^{198} is also probably more exclusively taken up by the reticulo-endothelial cells than non-colloidal iron. The method should also be useful for other studies of reticulo-endothelial activity.

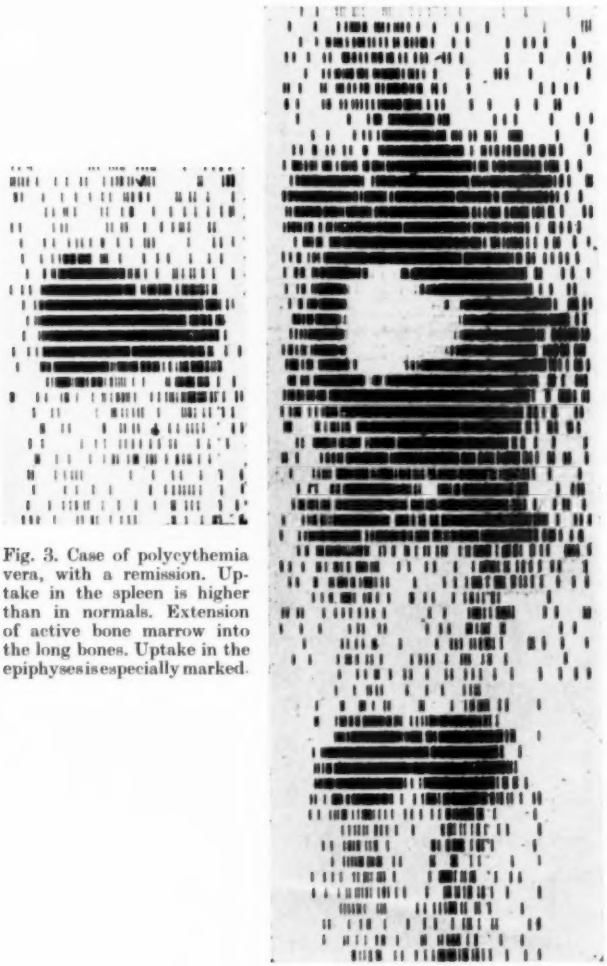

Fig. 3. Case of polycythemia vera, with a remission. Uptake in the spleen is higher than in normals. Extension of active bone marrow into the long bones. Uptake in the epiphyses is especially marked.

SUMMARY

The deposition in the liver, spleen, and bone marrow of colloidal Au^{198} injected intravenously was studied by means of scintillography. Cases of polycythemia whether in relapse or remission often showed a greater uptake in the spleen than normal cases. A high uptake in the long bones, particularly in the epiphyses, was noted and suggested that it may be possible to localize active bone marrow by this method.

ZUSAMMENFASSUNG

Die Ablagerung von intravenös injiziertem radioaktiven Gold (Au^{198}) in der Leber, in der Milz und im Knochenmark ist scintillographisch untersucht worden. Polycythaemiefälle zeigten sowohl bei Rezidiven als auch bei Remissionen oft eine grössere Anreicherung in der Milz als normale Fälle. Eine deutliche gesteigerte Anreicherung in den langen Röhrenknochen, besonders in den Epiphysen, wurde beobachtet und deutete an, dass es möglich sein dürfte, aktives Knochenmark mit dieser Methode zu lokalisieren.

RÉSUMÉ

La fixation dans le foie, la rate et la moëlle osseuse de l'or colloïdal Au^{198} injecté par voie intraveineuse a été étudiée par scintillographie. Des cas de polycythémie, en rechute ou en rémission, ont souvent présenté une fixation splénique plus importante que des sujets normaux. On a noté une fixation élevée dans les os longs, en particulier dans les épiphyses; ceci fait penser qu'il pourrait être possible de localiser la moëlle osseuse active par cette méthode.

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CENTRE ANTICANCÉREUX (DIRECTEUR: PROF. P. DESAIVE) DE L'UNIVERSITÉ DE LIÈGE, BELGIQUE

ÉTUDE DOSIMETRIQUE ET CLINIQUE DE LA RADIOTHÉRAPIE A TRAVERS GRILLE

par

André Herve et *Roger Ghys*

C'est en 1909 que KÖHLER proposa d'interposer sur le trajet des rayons roentgen entre l'ampoule et la peau du malade une plaque métallique percée de trous de 1 à 2 mm de diamètre; ainsi le point d'entrée de chaque faisceau serait extrêmement petit et l'on pourrait atteindre une nécrose cutanée sans plus de conséquences que celles des minuscules brûlures du thermocautère. De cette façon, KÖHLER pensait pouvoir augmenter 5 fois la dose cutanée maximum. Il ne semble cependant pas qu'il ait mis sa méthode en pratique.

Ce ne fut qu'en 1933 que LIBERSON à New-York reprit l'idée du traitement à travers un écran perforé. Il est remarquable de constater qu'il en arriva, à la suite de ses expériences, aux normes admises actuellement: il conseillait de découper dans une feuille de plomb de 1.5 à 2 mm d'épaisseur des ouvertures circulaires de 8 mm de diamètre représentant à peu près la moitié de la surface de la feuille.

A cette époque HARING, en Allemagne, utilisa des grilles avec une idée de départ toute différente de celle de KÖHLER: il visait à réaliser en profondeur une inhomogénéité semblable à celle des implantations de radium. Il est le premier à avoir publié une série de résultats satisfaisants dans le cas de tumeurs profondes. Le terme «grille» a acquis droit de cité dans la littérature radiologique française, anglaise (grid) et allemande (Gitter). Cependant, il ne correspond pas à la réalité: dans la plupart des cas, il désigne des plaques perforées pour lesquelles le mot «crible» conviendrait mieux.

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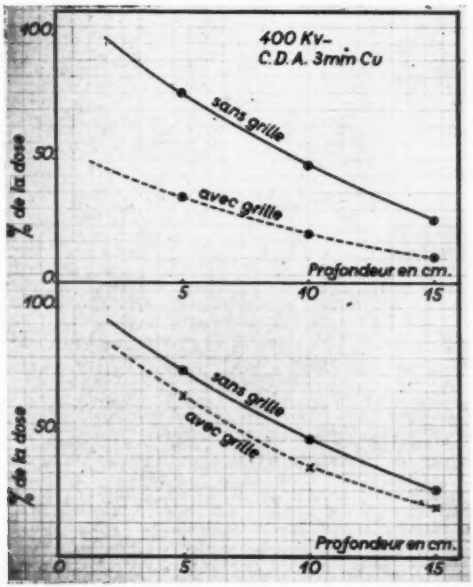

Diagramme 1. Rendement en profondeur avec et sans grille de plomb dans un fantôme de riz. *En haut:* Mesures expérimentales pour 100 r en surface — sans grille et avec grille. *En bas:* Rendement en profondeur en tenant compte du facteur de grille.

Grynkraut et Sitkowski étudièrent expérimentalement la question avec grilles mobiles et immobiles. Ils tentèrent d'établir un rapport optimum entre les zones couvertes et découvertes et montrèrent un effet de protection après irradiation totale à travers grille. Leurs travaux ne semblent pas avoir entrainé d'application clinique immédiate.

Depuis quelques années, le problème a été repris dans de nombreux pays. Deux conceptions théoriques continuent à s'affronter.

1. Celle de Köhler qui ne tient compte que de la protection de la peau et essaie de restaurer l'homogénéité du faisceau en profondeur. Dans cet ordre d'idée, Marks a publié son expérience clinique en 1952. Il souligne l'intérêt de la méthode pour augmenter la tolérance cutanée sans donner de précisions sur la répartition de l'énergie dans les tissus. Ce point a été abordé par Loevinger et Minowitz qui admettent que les difficultés rencontrées pour reproduire, à chaque séance, les mêmes conditions géométriques produisent à coup sûr une homogénéisation du rayonnement profond. Eichhorn et Matschke ne partagent cependant pas ce point de vue.

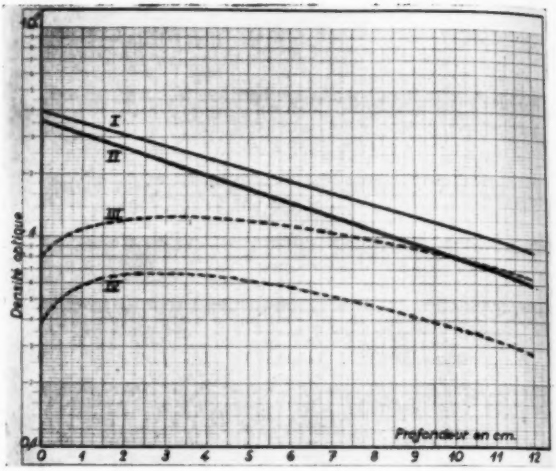

Diagramme 2. Mesure sur film de la densité optique en fonction de la profondeur dans un fantôme de cire Columbia (C. D. A. 3 mm Cu, champ 10 × 15 cm) à travers une grille de caoutchouc plombé de 9 mm. Courbe I — En dessous d'une ouverture centrale; II — En dessous d'une ouverture périphérique; III — En dessous d'une zone couverte centrale; IV — En dessous d'une zone couverte périphérique.

2. Celle entrevue par HARING et devéloppée par JOLLES. Pour cet auteur, il n'est pas interdit de conserver en profondeur l'inhomogénéité du faisceau de rayons roentgen. Il a montré avec MITCHELL que l'inhomogénéité persiste bien qu'elle diminue en fonction de l'épaisseur traversée, à cause du rayonnement secondaire. Il postule que des facteurs diffusants provenant de zones fortement irradiées empêchent la croissance de cellules néoplasiques situées quelques millimètres plus loin, dans une zone protégée. De plus, la persistance d'un tissu conjonctif peu touché favoriserait la limitation de la croissance tumorale et le processus de régénération des tissus sains.

De nombreux problèmes se posent au radiothérapeute qui adopte cette méthode, mise à l'étude depuis cinq ans dans notre service avec un générateur de 400 kV. Nous présentons ici l'état actuel de nos observations.

I. Mesures physiques

Ces mésures ont été effectuées afin de préciser le degré d'homogénéité obtenu à diverses profondeurs avec notre technique d'irradiation.

Matériel et méthodes. Constantes physiques: Générateur à tension pulsatoire (Maximar G. E.) 400 kV, 5 mA, filtre 1 mm Cu et 1 mm Al. Distance focale 70 cm. Champ 10 × 15 cm. Grilles: Surface protégée 60 %, perforations circulaires de 1 cm de diamètre, distance entre les centres des deux perforations 1.5 cm. Une grille de plomb de 2.5 mm d'épaisseur et une grille en caoutchouc plombé de 9 mm d'épaisseur ont été utilisées. La transmission du rayonnement direct à travers le plomb est de 2 % et à travers le caoutchouc plombé de 10 %.

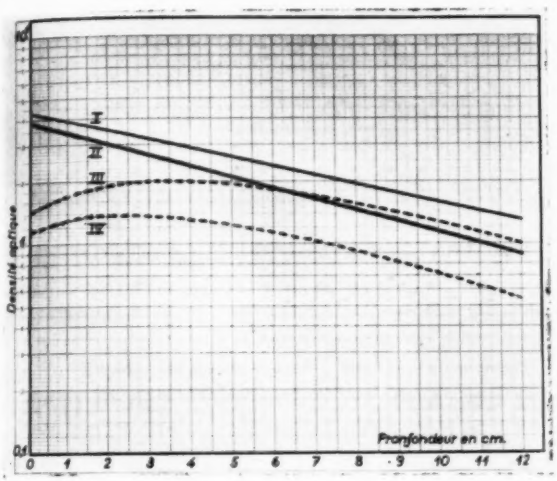

Diagramme 3. Mesure sur film de la densité optique en fonction de la profondeur dans un fantôme de cire Columbia (C. D. A. 3 mm Cu, champs 10 × 15 cm) à travers grille de plomb de 2.5 mm d'épaisseur. Courbe I — En dessous d'une ouverture centrale; II — En dessous d'une ouverture périphérique; III — En dessous d'une zone couverte centrale; IV — En dessous d'une zone couverte périphérique.

Dosimétrie: Fantôme de riz ou de cire, dosimètre universel Siemens, films radiophotographiques Ilflex sans écran.

Photométrie: Photovolt — Co. Mesure des films Ilford exposés pendant 2 secondes, développés simultanément pendant 4 minutes dans le révélateur à grains fins I. D. 19. (Nous remerçions la firme Ilford qui nous a fourni la courbe de noircissement de ce type de film exposé à un rayonnement équivalent. Entre une densité optique de 1 et 3.5 la réponse de ce film est pratiquement linéaire. On peut donc admettre que le noircissement du film en un point donné est une mesure de la dose reçue en ce point.)

Conduite des expériences. Nous avons étudié la transmission en profondeur au moyen d'un dosimètre placé à différents niveaux dans un fantôme de riz et comparé les résultats obtenus avec et sans grille.

Dans une seconde série d'expériences, nous avons intercalé dans un fantôme de cire, une série de films radiographiques et procédé sur ceux-ci à des mesures photométriques.

Résultats et discussion des expériences

Le diagramme 1 représente les résultats des mesures en profondeur avec et sans grille.

La transmission étant d'environ 50 % à travers la grille de caoutchouc plombé, de 42 % à travers la grille de plomb, il est donc nécessaire de doubler le temps d'irradiation pour distribuer la même dose que par la méthode habituelle. Le rendement en profondeur est légèrement inférieur à celui de l'irradiation classique, et, contrairement à ce que les courbes pourraient faire croire, il n'existe pas d'homogénéité profonde; a chambre d'ionisation étant plus grande que les orifices de la grille réalise une sommation des doses entre différents points. Pour mettre ce

fait en évidence, la méthode photographique est beaucoup plus démonstrative. Les diagrammes 2 et 3 montrent que le rayonnement reste inhomogène à toute profondeur utile en thérapeutique malgré le rôle joué par le rayonnement diffusé. Ce dernier passe par un maximum à 3 cm de profondeur tant pour la grille de plomb que pour celle en caoutchouc plombé. Il diminue ensuite de façon à peu près parallèle au rayonnement direct. On n'observe pas d'égalisation entre deux zones immédiatement voisines couvertes et non couvertes. Un point mérite de retenir notre attention: le rayonnement *diffusé* central devient supérieur en valeur absolue au rayonnement *direct* périphérique à partir de 6 cm de profondeur pour les grilles en caoutchouc et de 10 cm pour les grilles de plomb.

Nous avons vérifié cette persistance de l'effet grille chez l'homme, en interposant entre la grille et la peau 7 cm de cire et en distribuant 1,000 r à la peau (qui se trouvait ici dans la position d'une tumeur profonde). La réaction cutané dessina un pointillé érythémateux très net (Fig. 1).

La majorité des auteurs ont obtenu des résultats assez comparables. Depuis les premières recherches de LOEVINGER et MINOWITZ, JOLLES et MITCHELL ont fourni en 1952, des courbes isodoses bien démonstratives.

SOPP et STANTON ont étudié, pour des C. D. A. de 1.10 et de 1.82 mm Cu, l'importance du diamètre et de la disposition des orifices de la grille et proposé des orifices de 1.5 cm de diamètre, disposés selon un réseau triangulaire; ils ont obtenu au moyen de microchambres des isodoses comparables à celles de JOLLES.

Pour SEIDEL la variation du diamètre des ouvertures de la grille n'a pas d'influence sur la dose profonde et son inhomogénéité si le rapport entre surface couverte et découverte reste constant.

STRELINE a étudié les réactions cutanées chez le lapin avec différents types de grilles. Il conseille des grilles à orifices très fins, assez semblables au premier type de KÖHLER. GROS et coll., travaillant avec une C. D. A. de 1.3 Cu, ont repris les expériences de LIPPMAN et JACOBSON. Ils ont obtenu, avec un dosimètre à grande chambre, une courbe semblable à celle de notre Diagramme 1 et avec des microchambres, une courbe voisine de celles de nos Diagrammes 2 et 3. Ils n'ont pas étudié les phénomènes en périphérie du champ.

Plus récemment, des tables ont été présentées par SCHRÖCK-VIETOR, SEIDEL, WACHSMANN et DIMOTSIS; SEIDEL admet qu'il est possible de distribuer à travers grille sur de larges champs, une dose 5 fois plus forte qu'avec une irradiation classique. La cyclothérapie permet d'obtenir des doses focales aussi élevées, mais dans un volume beaucoup plus petit. Les appareils de téléthérapie au Co^{60} dont un des avantages est la possibilité d'irradier de grandes surfaces avec un faisceau homogène, seraient

à ce point de vue plus intéressants. BECKER et coll. ont étudié l'application de la grille aux rayons roentgen ultra-durs et au rayonnement β d'un betatron de 15 MeV, tandis que KUTTIG et MEIER l'ont appliquée à la radiothérapie superficielle (méthode de Chaoul). Dans le cas des rayons γ du betatron, il n'y a pratiquement pas d'homogénéisation à 25 cm de profondeur; au contraire, pour les rayons émis sous 60 kV et pour le faisceau électronique du betatron, l'homogénéisation est presque parfaite à 4 cm de profondeur.

L'effet grille en profondeur ne fait donc pas de doute bien qu'il existe une atténuation de la différence entre les zones couvertes et non couvertes au fur et à mesure que le rayonnement pénètre dans les tissus. Il est accentué par l'élimination du rayonnement diffusé et par l'utilisation de grilles suffisamment absorbantes.

II. Résultats cliniques

Comme le font remarquer EICHHORN et MATSCHKE, les deux conceptions théoriques signalées plus haut, et qui sont à la base de la technique des grilles, peuvent recevoir une application pratique et s'accomodent l'une et l'autre de l'inhomogénéité constatée. Il semble bien à ce point de vue que la question de dose soit primordiale:

ou bien on donne une dose énorme (MARKS) et l'on obtient dans les zones couvertes un rayonnement diffusé tel que le tissu tumoral puisse être détruit, mais il est illusoire d'espérer dès lors une protection du conjonctif;

ou bien on s'en tient à des doses relativement modérées (JOLLES) et l'on respecte dans le profondeur le tissu interstitiel. C'est cette méthode que nous avons adoptée.

Matériel et conditions d'irradiation

De 1953 à 1956, nous avons traité 69 malades à travers grilles plombées (75 traitements). Nous nous sommes adressés à des cas de mauvais pronostic soit qu'il s'agisse de tumeurs très malignes au départ, soit de récidives ou de métastases de néoplasies déjà traitées.

Les irradiations ont été faites dans les mêmes conditions techniques: 400 kV, filtration 1 mm Cu + 1 mm Al, D. F. P. 70 cm avec de très grands champs (15 × 15) et des portes d'entrée multiples. Nous nous sommes efforcés d'englober ainsi de larges territoires dans le faisceau. Les malades subissaient 6 séances d'irradiation par semaine, un champ étant irradié chaque jour. Les doses unitaires ont varié entre 300 et 800 r/séance, mesuré au dessus de la grille de plomb, déposée sur la peau. Le maximum par champ a été de 13,300 r.

Réactions cutanées

Elles se font en trois phases:

1. Un léger erythème apparait après quelques jours; si le traitement est interrompu, il disparait sans laisser de traces.

Fig. 1

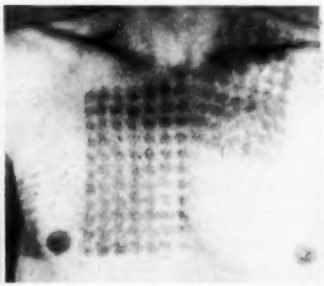

Fig. 2

Fig. 3

Fig. 1. Réaction cutanée observée sur la peau avec interposition de 7 cm de cire Columbia entre la source et la surface cutanée (ici dans la position d'une tumeur située à 7 cm de profondeur).

Fig. 2. Pointillé érythémateux obtenu après 3,000 r en environ 20 jours.

Fig. 3. Desquammation et pigmentation obtenues après 9,000 r en environ 2 mois.

2. Un érythème pointillé franc se dessine aux alentours de 3,000 r en 20 jours et évolue vers une épithélite subaigüe ou aigüe qui se manifeste aux environs de 7,000 r (45 jours) (Fig. 2). A cette épithélite fait suite une desquammation des zones irradiées laissant en place une peau saine, pâle, sur fond pigmenté. Ce stade est atteint après 2 mois au cours desquels le malade a reçu 9,000 r (Fig. 3).

3. Au delà de cette dose, on peut voir réapparaître un erythème puis une épidermité intéressant à la fois les zones couvertes et non couvertes (Fig. 4). Après 3 mois, il persiste encore sur la peau des zones de desquammation laissant en place des cicatrices nacrées, témoignant de l'atrophie définitive de la peau au niveau des trous de la grille. Il faut plusieurs mois pour que s'estompe la pigmentation des zones couvertes.

L'érythème est en général un peu plus précoce au niveau du thorax: il apparaît nettement aux environs de 2,500 r tandis qu'il faut atteindre 3,500 r au niveau de l'abdomen. Cependant, les variations individuelles sont importantes, et encore accentuées par la protraction variable du traitement.

Citons à ce propos le cas curieux d'un malade qui, recevant de la vitamine K à fortes doses pendant son traitement, developpa un érythème très marqué après une seule dose de 600 r, sur chaque champ. Par contre, un malade ne présenta qu'un érythème léger après 13,000 r/champ en 80 jours.

Si l'érythème est plus précoce sur le thorax, les réactions cutanées abdominales tardives sont souvent plus marquées: sur 8 radioépidermites graves, 6 se sont produites sur cette région: dans 5 de ces cas, le traite-

Fig. 4

Fig. 5

Fig. 4. Epidermite obtenue après 10,000 r en environ 2 mois.

Fig. 5. Sequelles tardives (un an) après 10,000 r en 106 jours sur l'abdomen.

ment dut être abandonné, après 4,800 et 8,500 r/champ. L'adiposité et l'humidité dans les plis sont des facteurs aggravants.

Nous avons observé deux complications lointaines. Un patient, 7 mois après avoir reçu 9,000 r a présenté une sclérose dermique très accentuée avec œdème de voisinage au niveau de la région pubienne. Une patiente fort adipeuse a développé en 5 mois et demi une sclérose marquée et, un an après la fin de traitement, une radio-nécrose des plis inguinaux et de la région sus-pubienne qui conduisit à une érosion des parois de l'artère fémorale droite. Elle avait reçu 10,000 r/champ (sur 5 champs) en 106 jours. Il a fallu avoir recours chez celle à un traitement chirurgical réparateur. Deux ans et demi après la fin des irradiations, cette radionécrose évolue bien mais est loin d'être cicatrisée (Fig. 5).

Nous n'avons jamais observé, dans notre service, de telles radionécroses après radiothérapie classique à 400 kV, même avec des doses considérables; il est vrai que dans ces cas, nous avons recours à de petits champs multiples.

Le recul de plus de 3 ans nous manque chez la plupart des malades, car presque toujours il s'agissait de cancers à un stade avancé. Il n'est pas interdit de penser qu'une longue survie entrainerait chez les patients irradiés à travers grilles un pourcentage important de sequelles graves.

Dans notre expérience, limitée dans le temps, nous n'avons pas à nous féliciter de l'effet esthétique et il est peu probable que les tissus irradiés puissent encore subir un traumatisme radiologique ou chirurgical. S'il est possible, comme MARKS l'a fait, de distribuer en moins d'un mois des doses cutanées supérieures à 20,000 r, nous pensons avec SILVERSTONE que cette technique peut amener de réelles catastrophes, puisque, avec des doses très inférieures, nous arrivons déjà à des résultats éloignés peu satisfaisants.

Il semblerait, d'après KUTTIG et MEIER qu'il soit préférable de terminer l'irradiation d'un champ donné avant de passer à une seconde porte d'entrée. Quelques cas traités suivant ce schéma nous ont montré que la réaction cutanée était aussi intense mais ne se marquait qu'après la fin de l'irradiation de ce champ. Quoiqu'il en soit, il nous parait opportun de souligner que les réactions des tissus superficiels consécutives à un traitement à travers grille entrainent des sequelles notables.

Réactions générales

Les réactions générales ont été modérées. Douze cas développèrent un mal des rayons plus ou moins typique en cours de traitement. Dans trois, cette symptomatologie fut à l'origine d'un abandon prématuré de la thérapeutique. Comme il s'agissait presque toujours d'une irradiation de très larges zones thoraciques ou abdominales, on doit admettre que la méthode est plus intéressante à ce point de vue que l'irradiation classique.

Dans cet ordre d'idées, RODÉ et BOZÓKY ont récemment décrit une technique d'irradiation totale et subtotale avec une grille de plomb incorporée au filtre. Ils seraient parvenus à distribuer 2,000 à 3,000 r à leurs malades sans provoquer de mal des rayons aigu. Ce phénomène peut être mis en rapport avec les récentes expériences de radiobiologie montrant l'importance de la protection de certaines zones corporelles dans la survie après irradiation létale.

Aperçu des résultats cliniques

Nous nous sommes efforcés de distribuer une dose tumeur minimum de 3,000 r sur les lésions lymphoïdes et de 5,000 r sur les épithéliomas. Nous avons parfois dépassé ces doses (le maximum a été de 9,500 r/tumeur).

Les cancers pulmonaires. Parmi les 21 malades traités, 17 étaient cliniquement ou radiologiquement inopérables, 4 étaient à la limite de l'opérabilité: Des 17 cas, biopsés, 5 étaient des épithéliomas épidermoïdes, 12 des épithéliomas anaplastiques. Immédiatement après le traitement, on nota une aggravation dans 6 cas, une amélioration

clinique, sans modification radiologique dans 6 cas, une amélioration clinique et radiologique dans 9 cas. Les résultats immédiats sont favorables, mais une récidive locale ou une métastase dans un organe vital assombrissent vite le tableau. Deux patients sont en vie, 4 sont morts en généralisation néoplasique, un pendant une tentative de pneumectomie et 13 de l'évolution locale de la tumeur qui se compliquait dans un cas d'une tuberculose évolutive et dans un autre d'une silicose à un stade avancé. La plus longue survie après la fin du traitement est de 12 mois. La survie moyenne des malades décédés (19) est de 4 mois après la fin du traitement, de 7 mois après les premiers symptômes. Pendant la même période, 103 cancers pulmonaires ont été traités à doses palliatives et 23 à doses curatives sans grilles: la survie moyenne dans les deux groupes a été de 12 mois depuis les premiers symptômes. Pour 37 cas non traités, elle fut de 10 mois.

Tumeurs médiastinales. Six cas de tumeurs lymphoïdes médiastinales ont été traitées, dont 5 sont en vie; le sixième, par contre décéda 9 jours après la fin du traitement.

Tumeurs du cou. Nous avons rangé dans le groupe une série d'affections d'origine diverse (1 épithélioma du larynx, 2 épithéliomas de l'amygdale, 3 tumeurs lymphoïdes malignes). Ces cas avaient d'importantes adénopathies cervicales; la radiothérapie fut conduite de façon assez semblable chez tous. Deux sont actuellement sans symptôme, deux ont été améliorés. Les deux derniers étaient tout à fait désespérés au départ (un sarcome de Hodgkin et un épithélioma de l'amygdale récidivant pour la troisième fois): ils moururent 5 et 48 jours après la fin de l'irradiation.

Tumeurs ovariennes. Huit patientes ont été traitées: 4 sont en vie: une récidive post-opératoire et 3 irradiations post-opératoires. Dans une de celles-ci, l'opération avait été incomplète: un semis de nodules péritonéaux subsistait; cependant la malade est aujourd'hui en bonne santé, 2 ans et 6 mois après la fin de traitement. Deux autres n'ont retiré aucun bénéfice du traitement: chez l'une on vit apparaître de l'ascite et des ganglions inguinaux pendant la cure de rayons roentgen, chez l'autre des métastases pleurales. La radiothérapie fut abandonnée et elles moururent peu après.

Cancers du corps utérin. Huit cas ont été traités, 1 stade III, 7 stade IV. On ne peut dès lors s'attendre à des résultats brillants. Six malades sont décédées en moyenne 5 mois après la fin du traitement, mais l'on nota chaque fois une amélioration sensible, tant objective que subjective. Deux patientes sont en vie, un stade III depuis 13 mois et un stade IV depuis un an et 3 mois.

Cancers du gros intestin. Six cancers du gros intestin (1 colon ascendant, 1 sigmoïde et 4 rectum) ont été soignés: 3 étaient

inopérables, les 3 autres étaient des récidives post-opératoires. Les résultats furent assez variables; dans deux cas, le traitement dû être interrompu et les patients moururent peu après. Chez deux on nota une considérable amélioration: elle ne dura que 80 jours chez le premier (cancer du rectum) et 14 mois chez le second (épithélioma du colon). Deux malades sont encore en vie depuis un an et 3 ans sans signe de récidive.

Nous avons en outre soigné: 2 métastases inguinales de cancer de la vulve, 2 métastases de cancer du sein, 2 cancers gastriques, 2 cancers prostatiques, 4 cancers de la vessie, 1 métastase de maladie de Hodgkin, 1 métastase de séminome, sans résultats dignes de commentaires.

Dans 21 cas, le traitement n'a pas eu d'effet sur l'évolution des tumeurs traitées; 32 traitements ont amené une regression transitoire. Dix-huit patients sont en vie: chez 8 d'entre eux (où la stérilisation de la tumeur ne paraît pas complète) le traitement remonte à trop peu de temps pour pouvoir juger du résultat final. Les 10 autres sont cliniquement guéris depuis 9 à 33 mois.

Ces résultats paraissent très comparables à ceux que l'on aurait pu obtenir dans une série semblable avec la radiothérapie classique énergiquement conduite.

Discussion

La plupart des auteurs n'ont irradié à travers grille que des cas graves, en s'attachant d'avantage à l'effet palliatif qu'à l'effet curatif. Aussi est-il difficile de se faire une opinion exacte sur les avantages que présente, *a longue échéance* un tel traitement.

Marks (1952) a traité 200 cas de tumeurs étendues avec des doses très élevées dépassant parfois 20,000 r/champ. Il a pu mener la thérapeutique à bien chez 102 patients. Il ne cite aucun résultat d'ensemble. Botstein et Harris ont traité 140 cas désespérés avec 24,000 r/champ en 28 jours. Cette méthode se serait révélée efficace surtout dans les cas de cancers étendus du poumon et de la vessie. Becker et Kuttig ont irradié 934 cas de tumeurs diverses, la plupart à un stade très avancé. Ils ne donnent pas leurs résultats globaux. Devois et coll. ont cité 13 cas avec des résultats palliatifs. Pfeifer et Seidel (1956) ont étudié l'action de ce traitement sur 40 cas de carcinomes bronchiques inopérables. Ils ne trouvent de survie importante que chez les malades ayant reçu de 7,500 à 12,000 r/tumeur. Enfin, Kahr, après avoir traité 56 cas de cancer du poumon, admet qu'il n'obtient rien de plus qu'avec les techniques classiques.

On peut regretter que les résultats publiés jusqu'à présent soient si peu explicites. Nous ne pensons pas que dans l'ensemble, ils soient brillants, à l'exception de quelques cas d'espèce.

Si la grille permet d'irradier plus facilement de très grands champs thoraciques ou abdominaux, elle entraine des réactions cutanées et des cicatrices assez disgracieuses. Nous avons observé plusieurs radio-epithélites aigues et une véritable catastrophe cutanée chez une patiente guérie de sa tumeur. Les réactions générales sont par contre moins marquées qu'avec la technique habituelle. La méthode ne se recommanderait donc que chez les malades en mauvais état général et en l'absence d'installation de supervoltage autorisant de grands champs.

Sans atteindre les 24,000 r prônés par certains auteurs, il semble recommandable d'administrer à la lésion au moins le double de la dose classique pour obtenir un résultat. Un effet palliatif est sans conteste enregistré mais est-il supérieur à celui qu'entraine d'autres méthodes. Il est difficile de se faire une opinion. Il est plus malaisé encore de se prononcer sur l'effet curatif.

Il nous paraît opportun de souligner qu'une thérapeutique à travers grille ne pourra jamais concurrencer un traitement par supervoltage (cobalt, accélérateurs linéaires, betatrons etc.) car à l'inverse de ces derniers: elle ne forme que des champs inhomogènes, elle ne résout pas le problème de l'absorption différentielle, elle n'améliore pas le rendement en profondeur; si elle permet d'administrer de plus fortes doses profondes, c'est au dépens des tissus superficiels dont les sequelles ne sont pas à l'abri d'accidents.

La technique des doses massives peu protractées éveille à cet égard notre médiance. Plus intéressant parce que plus biologique, le point de vue de JOLLES retiendrait davantage notre attention. On peut se demander si ce n'est pas sous cet angle qu'il faut poursuivre l'étude de l'irradiation à travers grille en n'accordant pas la première place à l'aspect physique du problème.

RÉSUMÉ

L'irradiation à travers grille réalise des champs inhomogènes en surface et en profondeur. Ce fait est démontré par mesures photométriques et dosimétriques à l'aide d'un appareil de 400 kV. Pour une même dose tumeur, les sequelles au niveau de la peau et du tissu de soutien sousjacent paraissent, à courte et longue échéance, plus importantes chez les malades traités à travers grille que chez ceux qui sont irradiés par les techniques classiques. Dans l'ensemble les résultats de notre expérience de 4 ans ne sont pas meilleurs qu'avec la radiothérapie classique. Jusqu'à nouvel ordre, cette technique paraît devoir être consacrée à quelques cas spéciaux, particulièrement lorsque l'on vise un effet palliatif sur des tumeurs très étendues.

ZUSAMMENFASSUNG

Die Gitterbestrahlung erzeugt inhomogene Felder auf der Oberfläche und in der Tiefe. Diese Tatsache wird durch photometrische und dosimetrische Messmethoden mit Hilfe eines 400 kV-Apparates demonstriert. Für die gleiche Tumordosis scheinen die

frühzeitig oder spät auftretenden Strahleneffekte in der Haut und dem darunter liegendem Stützgewebe bei den mit Gittertechnik bestrahlten Kranken ernsthafterer Art zu sein als bei den mit klassischen Methoden behandelten Patienten. Zusammengefasst sind die Ergebnisse unserer sich über 4 Jahre erstreckenden Erfahrungen nicht besser als mit der klassischen Radiotherapie. Bis auf weiteres scheint diese Methode nur für Spezialfälle geeignet zu sein, in welchen man einen palliativen Effekt auf sehr ausgedehnte Tumoren austrebt.

SUMMARY

Photometric and dosimetric measurements with a 400 kV unit have shown that the irradiation through a grid produces a non-homogeneous distribution of the skin and depth doses. For the same tumour dose, the immediate and later effects upon the skin and underlying connective tissue appear to be more severe for the patient with this method than when the conventional technique is employed. A survey of four years' results shows that they were no better with the former than with the latter. Subject to review in the light of further experience, it would seem that the grid technique should be employed only in those special cases where a palliative effect upon a widespread growth is required.

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BOOK REVIEWS

MAGNETIC REMOVAL OF FOREIGN BODIES. By Murdock Equen. 94 p., 119 figs. Charles Thomas, Springfield, Ill., 1957. $ 4.50.

The author of this book is an otorhinolaryngologist and describes his experiences in the removal of foreign bodies from the air passages, oesophagus, stomach, and duodenum. As is evident from the title, a magnet is mainly used when the foreign body is of attractable metallic material. The procedure has been successful in over 200 cases although 10 failures are also reported. The author employs Alnico permanent magnets (General Electric Company) in the form of rods measuring 3 mm in diameter and 35 mm in length, or 6.5 mm in diameter and 45 mm in length. Slightly curved magnets of the latter size are also used.

The book consists chiefly of a material of 78 cases. The metallic foreign bodies are detected and localized roentgenologically and removed by means of the magnet under fluoroscopic control. As no radiologic problems are dealt with in the book, it has little value from a roentgenologic standpoint. It will, however, certainly prove of interest to those upon whom may fall the task of removing foreign bodies from the bronchi and upper parts of the digestive tract, in spite of the text being 'written in an informal, conversational style', as stated in the blurb on the jacket.

Bengt S. Holmgren.

GRUNDLAGEN FÜR DIE MESSUNG DER STRÖMUNGSGESCHWINDIGKEIT DES BLUTES MITTELS EINER RÖNTGENKYMOGRAPHISCHEN MESSMETHODE. Von W. Güntert und E. A. Zimmer. 187 Seiten, 87 Abb. S. Karger A. G., Basel 1957. S. Fr. 25.—

A well-written and readable book which deals thoroughly with the existing methods of measuring the rate of the blood flow. The writers go through the various methods systematically and point out their advantages and disadvantages. Special attention is payed to a finer method of roentgenkymography, which is described as a valuable complement to other examinations of the heart and blood vessels. The greatest difficulty with this method was to find a contrast medium, the specific gravity and viscosity of which approached those of the blood, and which furthermore mixed well with the latter. After careful tests, the authors decided that 'low viscosity' Jodipur (an iodized oil), injected into the blood vessels in the form of a few droplets produced the best results. They themselves admit that this method is in the nature of a compromise but at the same time one which is well tolerated by the body without risk of fat embolism. The results reached are based mainly upon experimental circulation studies performed upon a fixed tube system with constant and pulsating flows.

The book is an authoritative one. The authors consider the problems with a critical mind and do not jump to hasty conclusions. The book is warmly recommended to all those engaged upon investigations of the blood circulation.

Sven Roland Kjellberg.

THE SALIENT POINTS AND THE VALUE OF VENOUS ANGIOCARDIOGRAPHY IN THE DIAGNOSIS OF THE CYANOTIC TYPES OF CONGENITAL MALFORMATIONS OF THE HEART. A ten year study of 421 angiocardiograms done on 283 patients. By Benjamin M. Gasul, Gershon Hait, Robert F. Dillon, and Egbert H. Fell. 80 pages, 41 illustrations and 2 tables. Charles C. Thomas, Springfield, Ill. $ 3.50.

This book contains nothing that has not been described before. The authors say that 'as far as we know, no previous attempt to establish the value of angiocardiography as a separate laboratory tool has been published previously'. Accordingly in their angiocardiographic examinations they have 'omitted any references to the clinical, roentgenologic, electrocardiographic, and cardiac catheterization findings' — a principle which the reviewer believes to be wrong. Angiocardiography is only one of a series of examinations necessary to clarify the whole pathologic complex present in congenital heart disease; it is best carried out last and directed by definite information obtained from previous clinical and roentgenologic investigations. Its aim should be to elucidate the pathologic anatomy as well as the haemodynamics of the heart. Angiocardiography performed as a routine measure and without consideration for the special problems obtaining in each individual case has little value. The authors are critical regarding selective angiocardiography (JÖNSSON et coll. 1949, KJELLBERG et coll. 1953) and state that it is more time consuming and dangerous than venous angiocardiography. Both premises are false. If the examination is linked with the heart catheterization, which must of course be performed in every case, it is no more time consuming than venous angiocardiography. Every angiocardiographic investigation and heart catheterization must necessarily entail certain risks by reason of the toxic nature of the contrast medium and the mechanical irritation exerted by the catheter upon the heart. The dangers are not lessened if the two examinations are performed upon different occasions rather than immediately following one another. It is on the other hand dangerous to carry out angiocardiography as an isolated procedure without regard to the other clinical findings and with no clearly defined objective.

No radiologist is numbered among the authors.

Gunnar Jönsson.

BOOKS RECEIVED

We acknowledge with thanks under this heading books received for review, which we trust will be regarded as a sufficient mark of appreciation of the courtesy of the sender. The reviews of selected items will appear as soon as opportunity affords.

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